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QUANTITATIVE ASPECTS OF THE RELATIONSHIP OF BIOLOGICAL MEASUREMENTS TO AGING PROCESSES

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Biologists have long distinguished between chronological age and physiological age; that is, they have recognized that at a given chronological age individuals will exhibit different tendencies toward death. Thus biological experience indicates that a population is a group of individuals who are undergoing physiological aging at some assortment of rates and that this physiological aging leads to death.

Obviously it would be very useful to be able to measure the physiological age or death tendency of individuals, since then those with a very high death tendency could be compared with those who have a very low death tendency in an effort to gain some insight into these aging processes. In a study of the evolution of coronary artery disease Gofman (2) introduced a highly effective approach to this problem. Gofman found that individuals who developed clinically manifest symptoms of coronary artery disease or who died from the disease had, on the average, higher concentrations of certain serum lipoproteins. However, there was considerable overlapping of the lipoprotein distribution of the two groups; that is, many individuals of the groups who did not develop clinically manifest disease or die of the disease had levels equal to or greater than those who did develop clinically manifest disease or die of it. At this point one could say qualitatively that higher lipoprotein concentrations were somehow related to coronary artery disease. In an effort to quantitate this relationship, Gofman divided the ordinate on the disease distribution by the ordinate on the non-disease distribution at the same lipoprotein concentration and thereby constructed a curve of probability of dying versus lipoprotein concentration. Thus here was a relatively simple method of quantitating the physiological age or death tendency in a population. Obviously by the inclusion of more biological measurements a more critical estimate could be made.

Furthermore it developed in this study of lipoproteins and coronary artery disease that the mean of those who died of the disease approached the mean of the remainder of the population as one went to the more advanced ages. In fact, if the study had been confined to individuals above 60 years of age, one might have concluded that no relationship existed. This is what would be anticipated if the lipoproteins were a measure of the rate at which individuals were developing death tendency. In other words, only individuals who were developing death tendency at a very high rate would die at younger ages, and as time went on individuals with lower and lower rates would be included. Thus it evolved from this study that ordinary statistical methods were not efficient in studies of aging, and a mathematical approach tailored to the particular needs of the problem was necessary.

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Since this represents a bounded mathematical problem, for each population and set of parameters the various solutions are unique. Thus one can predict the maximum relationship of any one variable as the number of equally related variables is increased, or one can predict the maximum relationship of all remaining measurements as the relationship of one is increased. The intent of this paper is to develop the mathematics and to discuss these relationships. In addition some mathematical models will be introduced to help illustrate these relationships.

MATHEMATICAL FORMULATION OF AGING

Two major categories of disease account for approximately 80% of the deaths in the United States at the present time. The number one killer is disease of the cardiovascular system, which accounts for 60% of the deaths, and number two is cancer, which accounts for 20% of the deaths.

Shown in figure 1 are curves of the death rates of these two disease categories plotted against age for white males. These are semilogarithmic plots, and it can be seen that the death rates are complex functions of time. In the simplest case where these curves could be represented by a straight line, the analytical function which would define the death rate is:

(I) $$D_t = D_o\, e^{Kt}$$

where: D = yearly death rate,
D_o = constant,
K = constant, and t = time

Equation I is often called the "Gompertz Function" (9) and expresses the fact that a population's death rate seems to double on a regular schedule with time. A population's yearly death rate is a measure of the probability that an individual from that population will die within one year. Equation I will eventually lead with time to the erroneous situation where the probability of death is greater than unity. Shown in figure 2 are these same death rates plotted against reciprocal time. A straight line on this plot would be given by the equation:

(II) $$D_t = D_o\, e^{-K/t}$$

Equation II is more acceptable on fundamental grounds because it does not lead to the situation of a probability greater than unity. Furthermore it can be seen that above 30 years of age these death rates are better represented by straight lines in figure 2 than in figure 1. Also a plot such as figure 2 allows a more reasonable extrapolation to the maximum death rate at infinite time. The significance of this will be discussed later.

These simple laws, as well as the more complex curves, state that the individuals of a population die at an increasing rate with age. Thus either (a) individuals are more susceptible to disease as they grow older, or (b) many diseases run a course in time, or (c) both factors are prominent in determining these death rates. The latter is obviously the most practical choice since included in the first is some underlying process like the second. Therefore, it can be conceded that death is generally the result of some aging process or processes which impair the organism to such an extent that death ensues or leaves the organism easy prey for some one or combination of processes (diseases), random or otherwise, which are endemic to the population. For the present at least we need not be concerned with what is meant by aging or an aging process; the terms can be merely concepts which convey to us the accumulation of probability of dying, which the death rate curves show is a consequence of time. The premise is, then, that the nature of these death rate curves is controlled by physical laws which govern physical processes and that, through use of these laws, reasonable predictions of coming events can be made.

Thus it is assumed that death in a human population is as predictable as the decay of radioactive atoms. One can, on the basis of some set of physical parameters,

arrange individuals into groups which differ in death rate much the same as the atoms can be grouped as elements and isotopes which differ in rate of decay. An array of physical measurements on the various atoms led to a knowledge of the structure of stable and unstable atoms. In an analogous manner, an array of measurements on individuals should lead to a knowledge of the nature of the "well" and "diseased" individuals.

The foregoing would then suggest that, even though such an equation as I defines the probability of death for a population as a whole, it need not be representative of each and every individual in the population; but rather, it averages the experience of all the individuals and is the natural first choice for any individual or group of individuals where accessory information is lacking. Indeed, it can be shown that subsegments of a population will have laws different from that for the whole population. For example, Dublin and Marks (1) have shown that overweight individuals have twice the mortality at all ages as compared to underweight individuals. At any given age one would therefore predict too high a death rate for those who are underweight and too low a death rate for those who are overweight, unless the weights were taken into consideration. In terms of rational medical practice, the basis for this weight effect on disease processes is of extreme importance, because it seems as though these aging processes, which lead to accumulation of probability of death, are proceeding at twice the rate in the overweight individual. An understanding of the nature of this effect of weight should lead to information concerning these underlying disease processes.

Through the use of other parameters besides age and weight, the population can also be segregated on the basis of death rates: blood pressure (4), serum lipoproteins (2), blood glucose (8). If one considered all these measurements simultaneously and each was independently related to the death rate then one could better characterize the individuals of the population with respect to death rate. Throughout this paper death rates will usually be discussed with respect to specific causes but it should be remembered that these are just special cases of the over-all death rate.

For the purpose of discussion an arbitrary function "T" (physiological age) will be introduced. "T" can be defined as a discriminating function which best separates a population on a scale of death rates, and is a combination of an arbitrary number of measures. This can be expressed as follows:

(III) $$D = f(T)$$

where D = yearly death rate

(IV) $$T = f(n_1, n_2, n_3, \ldots\ldots n_x)$$

If the population were stratified on the basis of some parameter (n_1), and the death rate for the entire population for some specific cause of death and for various subsegments (strata on the variable n_1) of the population were compared, there would be two possible outcomes: (a) the values of "D" for the various subsegments could demonstrate no systematic variation from the value of "D" for the entire population or (b) they would show a systematic variation.

The interpretation of outcome (a) would be that the disease process is random with respect to the parameter "n_1" or, in other words, that "n_1" is unrelated to the disease state. The interpretation of outcome (b) would be that the parameter is somehow related (directly or indirectly) to the disease process. The intrinsic quantitative relationship of a parameter to the disease process should be measured when all other related parameters are held constant and this can be expressed as:

(V) $$I_{n_1} = \left(\frac{dT}{dn_1}\right)_{n_2, n_3, \ldots n_x}$$

where I_{n_1} represents the intrinsic relationship between the variable "n_1" and the disease. These equations follow from V:

$$\text{(VI)} \qquad dT = \left(\frac{dT}{dn_1}\right) dn_1 + \left(\frac{dT}{dn_2}\right) dn_2 + \cdots + \left(\frac{dT}{dn_x}\right) dn_x$$

$$\text{(VII)} \qquad \frac{dT}{dn_1} = \left(\frac{dT}{dn_1}\right) + \left(\frac{dT}{dn_2}\right)\frac{dn_2}{dn_1} + \cdots + \left(\frac{dT}{dn_x}\right)\frac{dn_x}{dn_1}$$

Equation VII can be stated as: The total correlation between "n_1" and "T" is equal to the sum of its intrinsic correlation plus the sum of a number of terms which are due to the correlation of "n_1" with the other factors which also have an intrinsic correlation with "T."

The implications of equations V, VI, and VII are that, if it is found that there are n parameters which stratify the population with respect to death rate, and one wishes to decide which are the most strongly correlated, the most effective way of doing this is to take into account the various intercorrelations which exist.

It may well be that many variables will stratify the population with respect to death rate, and yet not be related to the disease, but are able to do so because they are correlated with a parameter which is related to the disease. Furthermore, a variable may have a total correlation which is greater or less than its intrinsic correlation as a result of its intercorrelation with other effective parameters.

In addition, having a group of parameters which are independently correlated with a disease death rate, it would be desirable to group them into a composite measure in order to obtain the closest estimate of an individual's probability of death. Here again this should be done in accordance with equation VI and only the independent contribution from each parameter should be combined into the composite measure. Calculated in this fashion, "T" would then be the best estimate of an individual's disease risk or mortality risk.

Since the function "T" is developed for the purpose of studying the effect of aging processes on disease incidence or death rate, it is imperative that the relationship between "T" and age be understood or that the relationship between "T" and "D" be independent of age. Therefore, the value of "T," to be of use in this respect, should include a measure of the extent to which disease (or aging) processes have progressed (or have made the organism susceptible to a disease). The nature of the death rate curves suggest that these disease or aging processes are proceeding at some assortment of rates within the individuals of a population. An individual's age is simply a measure of the time over which the process has developed. The extent to which the process has progressed would be $\int_0^t (\text{rate})dt$. Consequently, if the function "T" includes a measure of the extent of all the time-related processes in a disease state, then

$$\text{(VIII)} \qquad \left(\frac{dD}{dt}\right)_T = 0$$

Equation VIII therefore is an important test for the function "T." If equation VIII is not satisfied, there is some time related process not adequately accounted for in the measurement of "T."

The various parameters (n_1) can fall into the following 5 classes with respect to the aging process: (a) those which are not correlated with any aspect of an aging process, (b) those which are correlated with the extent to which an aging process has progressed, (c) parameters which are a direct measure of the extent to which an aging process has progressed, (d) parameters which are a direct measure of the rate of progression of an aging process, and (e) parameters which are correlated with the rate of progression of an aging process.

The last two classes (d) and (e) would have a special relationship to "T" which would be:

$$\text{(IX)} \qquad \left(\frac{dT}{dn_1}\right) = f(t)$$

For these classes it would be necessary to alter the parameter to include the time relationship and thus write:

$$\text{(X)} \qquad n_1' = f(n_1, t) \quad \text{then} \quad \left(\frac{dT}{dn_1'}\right) \neq f(t)$$

Assuming that some function "T" for a particular disease were developed which is a combination of n independently correlated measurements, the function could then be used to predict disease hazard with greater precision than any of the parameters taken individually. Furthermore it would represent, at any given time, with respect to our state of understanding of the disease process, the most precise measure of risk. As an individual's value of "T" increased, so would his probability of death. The very low values of "T" would have an attendant probability close to zero. The very high values of "T" would have an attendant probability close to unity. In other words a distribution on "T" would stratify the population into a continuous series of death rates. Therefore, at the point when the optimum precision in the measurement of "T," and hence disease risk, is reached, the distribution of "T" for a living population at some age, when compared with the distribution of "T" for those who die of the disease at that age, will present a situation similar to that of figure 3.

Prevalent in the literature of the medical sciences today is an attitude toward a set of distributions like those of figure 3. The statement will be made that since so many of the living have values of "T" equal to and even higher than those who die, this value of "T" has no significance to the disease. If we were to change the dn/n in figure 3 to dI/I, "T" to wavelength, living to aluminum and dying to magnesium, then the above statement would become: Since the curves for the two elements overlap, the intensity of the spectral lines has nothing to do with the nature of the atom. The physicists would say that is ridiculous, because inherent in this overlap is the explanation for the fine structures of the atom. This is true also for the disease case, and contained in this overlap is an understanding of the competing factors in the disease state.

With the passage of time these curves should overlap to a greater and greater extent. The degree of overlap is a measure of the death rate, and, as the death rate curves show, this increases exponentially with time. Therefore, in very old individuals, who must have a very high average death tendency, these two distributions should approach superimposition and, in such a case, ordinary statistical approaches would lead one to postulate that this measure was not significant to the disease even though this superimposition of distributions represents part of the proof of significance. Consequently, it would be unfortunate if a study of a variable's relationship to a disease process were confined to one age group and particularly so if this were an older age group. It is therefore incumbent upon the investigator to study his variable on as wide an age range as possible and then to stratify the population in, at most, decade limits to secure the information which is age-dependent.

One curve in figure 4 represents an abstract distribution of "T" for a living population. The other curve represents those individuals who will die of a disease within one year. At any value of "T" the probability of dying within one year is simply the number of individuals with that value of "T" who will die divided by the number of individuals who have that value of "T," or the ordinate on the diers' curve divided by the ordinate on the population's curve. Thus it is possible from a set of curves such as those of figure 4, to construct a curve of "T" versus death risk. The slope of this curve is a quantitative measure of the relationship of "T" to the disease.

It is not practical to obtain such a set of curves as those of figure 4 on the entire population, but a practical approach is to obtain a random sample of a reasonable size. What a reasonable size amounts to numerically will depend upon the particular problem being investigated. Obtaining a sample of a reasonable size of those who will die within one year without sampling a large segment of population is a genuine experiment in clairvoyance or at least would be if deaths from diseases were like deaths from impact with falling meteors.

The problem of obtaining a reasonable sample of individuals who will die of a particular disease is made somewhat easier by the fact that, prior to death, clinical manifestations of the disease usually appear. The assumption can be made that those who die from the disease have the same distribution as those who are living with clinical symptoms of the disease. This assumption is generally quite valid since these people make up the bulk of those who die from the disease. For predicting morbidity this group with clinical signs would need no qualifying assumptions except that they are a random selection.

Using a reasonable sample of individuals who have manifest clinical symptoms of the disease and a reasonable sample of individuals who do not have manifest signs, one could construct a set of distribution curves similar to those of figure 3.

In this case the ratio of the ordinate of the diseased curve to the ordinate of the non-diseased curve is the relative probability of developing the disease (or, with the above assumption, dying of the disease). Having a particular value of "*T*," the absolute probability of dying within one year from the disease would be:

$$P = \left(\frac{N_D}{N_L}\right)_T \left(\frac{\Sigma N_L}{\Sigma N_D}\right)(M) \quad \text{(See Apperdix)} \tag{XI}$$

where $\left(\frac{N_D}{N_L}\right)_T$ = the ratio of the ordinate at "*T*" on the diseased curve to the ordinate at "*T*" on the non-diseased curve.

$\left(\frac{\Sigma N_L}{\Sigma N_D}\right)$ = the ratio of the total number of people in the non-diseased group to the total number in the diseased group,

and (M) = the population yearly death rate

If "*M*" were the disease incidence rate per year, then "*P*" would be the probability of developing clinical sequela of the disease within one year.

Eventually, in order to justify fully the use of the group with manifest clinical symptoms in the development of the disease risk curve, it will be necessary to show that there is no change in the value of "*T*" upon the development of manifest symptoms. Therefore the point is reached where one has to select those who develop clinical sequela of the disease from the population and measure their "*T*" values before the incident occurs and again after the incident. Here again the problem of sampling a large segment population is encountered.

Part of this difficulty can be circumvented by the expedient of sampling a population subsegment known to have a large disease incidence rate and thus lessen the number of individuals that have to be sampled. This can best be accomplished by choosing an older age group as a sampling medium. The number of individuals necessary for the study then depends upon the disease incidence rate. But even here the obvious objection could be raised: Can one be certain that the findings in this older age group parallel the findings in younger age groups? As a result, a full scale population study may be necessary to quiet the last objection.

In an actual study, the formula for the function "*T*" would be derived from an analysis of the relationship of the parameters to the probability of death. In fact the function "*T*" may not even be calculated because the probability of death should be a unique function of "*T*" and as such could be used in place of it. The quantitative relationship between the values of a measurement and the death rate are obtained

through the use of equation XI and can be represented by a curve of probability of death versus the values of the measurement. Once the relationships of all the measurements to the death rate and the relationships of the measurements to each other have been determined, the probabilities can be combined according to the following equations which are derived in the Appendix:

(a) For those variables which are stochastically independent:

$$\text{(XII)}\quad P(D/n_1, n_2, \cdots n_x L) = \left[\frac{1}{P(D/L)}\right]^{x-1} P(D/n_1 L)P(D/n_2 L) \cdots P(D/n_x L)$$

Where: $P(D/n_1, n_2, \cdots n_x L)$ is the probability of dying, given that one is a member of the living population and possesses a particular set of values for the various parameters.

$P(D/n_x L)$ is the probability of dying, given that one is a member of the living population and has a particular value of parameter "n_x". This is the value derived from Equation XI

$P(D/L)$ is the population's yearly death rate.

(b) For those variables which show a correlation with one or more of the other parameters:

$$\text{(XIII)}\quad P(D/n_{x+1}, n_{x+2}, \cdots n_{x+y} L) = P(D/n_{x+1} L)\,\frac{P(n_{x+2}/n_{x+1} D)P(n_{x+3}/n_{x+1}, n_{x+2} D)\cdots}{P(n_{x+2}/n_{x+1} L)P(n_{x+3}/n_{x+1}, n_{x+2} L)\cdots}\,\frac{\cdots P(n_{x+y}/n_{x+1}, n_{x+2}, \cdots n_{x+y-1} D)}{\cdots P(n_{x+y}/n_{x+1}, n_{x+2}, \cdots n_{x+y-1} L)}$$

$P(n_{x+3}/n_{x+1}, n_{x+2} D)$ is the probability of having a particular value of the parameter (n_{x+3}) given that one is a member of the population of diers and has a particular set of values for the other two parameters. These various terms are analogous to the 1st, 2nd, 3rd, etc. order partial correlation coefficients.

(c) Equation XII and XIII can be combined according to:

$$\text{(XIV)}\quad P(D/n_1, n_2, \cdots n_{x+y} L) = \left[\frac{1}{P(D/L)}\right] P(D/n_1, n_2, \cdots n_x L)P(D/n_{x+1}, n_{x+2}, \cdots n_{x+y} L)$$

In an experimental situation equation XIII would present a formidable barrier to the solution of the individual probabilities, since it would require ordering the population on all the possible combinations of the correlated parameters and reduce the population to a series of small groups from which the magnitude of error, due to the small number in each group, could be very large. A practical solution to this dilemma is of course to make approximations, such as exclusion from Equation XIII of variables with low order correlations. The degree to which approximations will have to be made will depend upon the size of the population and the number of measurements. However, the point is not only to measure the probability of death with precision but also to comprehend the association of the parameters with the disease process.

At this point some mathematical models will be introduced for the purpose of illustrating the further development of the concept. In each of the models presented the base population will be normally distributed (in a statistical sense) on the variables used at age zero. The range of the parameters shall be from 50 to 150 units with a mean of 100 and a standard deviation of 10 units. The populations shall be considered as concentrated at values of the parameters divisible by 5. The relationship between the death rate and the parameters in the models in all cases has the form: $e^{-K/t}$. This formulation was used as it is consistent with equation II. In reality the equation can take on any form with the boundary conditions that D lie between 0 and 1. The form of the equation in any case would only change to numbers obtained. The general aspects will not be altered. All integrations were carried out on IBM computing equipment using the trapezoidal rule with $\triangle t = 1$. In the models K, C, a, and b are constants and D is the yearly death rate. The variable mean of 100 was chosen quite arbitrarily, but the reader can appreciate that many biological measurements such as weight, blood pressure, and blood glucose fall in this range. The values of the constants were chosen so that, in the first two models, they would give death rate curves similar to those of figure 2.

Model I. Only a time-related parameter is assumed to exist. The population is distributed on a variable n_1 which is considered to be the rate at which the time-related parameter is developing such that $P(D/n_tL) = e^{-K/n_t}$ and $n_t = n_1 t$; $\frac{dn_1}{dt} = 0$ with K = 12,000 and 24,000. The population death rate plotted against $1/t$ on a semilogarithmic scale is given in figure 5.

Model II. In addition to the time-related parameter of Model I, a non-time related parameter is considered. This variable is stochastically independent of n_t and n_1 and its relationship to the death rate is given by $P(D/n_2L) = Ce^{-a/n_2}$. The value of "C" is so adjusted that the value of $P(D/n_2L) = 1$ when the value of $n_2 = 150$, the maximum value it assumes in the distribution. Given in figure 5 are the semilogarithmic plots of the death rate versus $1/t$ for "K" of Model I equal to 24,000 with "a" above equal to 100 and 200.

Model III. Again only a time-related parameter is considered. In this model its rate is considered to increase exponentially with time according to $n_1 = n_0 e^{bt}$ with $b = \frac{\ln 2}{60}$. Again $\frac{dn_t}{dt} = n_1$ and hence $n_t = \frac{n_0}{b}(e^{bt} - 1)$. The probability of death is given by $P(D/n_tL) = e^{-K/n_t}$ with K = 24,000. Shown in figure 6 is the semilogarithmic plot of the death rate versus $1/t$.

Model IV. This model is identical to Models I and III except that the original values of the parameter are each reduced by 10%. The value of "K" is 24,000. Shown in figure 6 are the semilogarithmic plots of the death rates versus $1/t$ for the two death rate functions in this model.

DISCUSSION OF MODELS

Model I represents the simplest form of a population death rate function. These curves extrapolate to a death rate of unity at infinite time. Obviously the slope of the curves will depend upon the distribution of rates in the population and upon the value of "K."

Model II is representative of the effect of a non-time-related parameter on a death rate function. The net effect is to reduce the over-all death rate by some factor dependent upon the distribution of this parameter and its relationship to the death rate. The stronger the relationship and the broader the distribution, the greater will

be its effect on the death rate. In figure 1 a value of "a" = 100 caused a reduction in the death rates of Model I by approximately 30% and a reduction in the maximum rate at infinite time to 0.7. A value of "a" = 200 caused a reduction of 50% and a maximum rate of 0.5. The slope of the curves, however, remains constant. Whereas a change in the distribution of the time-related parameter causes a change in the slope of the death rate versus $1/t$ curve, a change in the distribution on this non-time-related parameter should change the intercept at infinite time but not the slope. In the curves of figure 2, heart disease extrapolates to a death rate of unity at infinite time, while cancer extrapolates to approximately 0.5. This can be interpreted as meaning that non-time related parameters seem to have a much more substantial contribution to cancer mortality, while with heart disease there seems to be little dependence upon such non-time-related parameters.

Extrapolation of the death rate curve of Model III to infinite time leads to a death rate greater than unity. This occurs because $1/t$ is not the proper function of time to use in plotting the death rates of this model if one uses a straight line for extrapolation. If, however, this model had included an appropriate non-time-related variable, the death rate could have been reduced such that extrapolation in figure 6 could have seemed reasonable because it would have led to a death rate less than unity. Thus one has to be cautious about interpretation of the death rate curves, because, given enough parameters and a full swing of possible relationships, an unending chain of models which fit the curves of figure 2 could be forthcoming.

Model IV, besides illustrating the effect of a change in distribution on the death rate curves, is an example of what might be anticipated if a therapeutic regimen, designed to reduce each individual's rate of aging by 10%, were applied to a population with these death rate relationships. The death rates for all ages were reduced by approximately 50% and, as a result, more individuals lived to advanced ages as shown in table 1.

Model IV also illustrates the point that differences in rate of aging are more easily detected at the lower ages where these curves are more separated. Furthermore, it indicates that changes in rate of aging are associated with a change in slope but not the intercept.

In an actual experimental situation, the various relationships to the death rate will come from an analysis of the experimental data, and these models may never find a counterpart in reality. However, they are sufficient to illustrate some of the salient points in an aging process which should aid in the analysis of any actual data.

The curves of probability of dying at ages 30, 50, and 70 as a function of the values of the non-time-related parameter of Model II with $a = 200$ are plotted in figure 7. These curves have the same slope, but the intercept at $1/n = 1/150$ increases with increasing ages. This occurs because the population is aging and, with time, becomes distributed over a higher and higher range of values of the aging parameter. In the limit when the entire population has progressed to an infinite amount of aging, this curve will have an intercept at unity. The curve is defined at this point by the following equation:

$$P_A(D/n_2L) = Ce^{-a/n_2} \tag{XV}$$

$P_A(D/n_2L)$ will be called the absolute probability of parameter n_2. It is measured when all other related parameters are at their maximum, where $P_A(D/n_1L) = 1$.

In figure 8 are the curves of probability of dying at age 30 as a function of the aging parameter with $K = 24{,}000$. One curve is that obtained in Model I, with no non-time-dependent variable, and the other is that for Model II with the non-time-

dependent parameter for which $a = 200$. These two curves are related through the following equation:

$$\text{(XVI)*} \qquad P(D/n_1L) = P_A(D/n_1L)\left[\sum^{n_2} \frac{N_L^{n_1 n_2}}{N_L^{n_1}} P_A(D/n_2L)\right]$$

$P(D/n_1L)$ is the measured probability of Model II and $P_A(D/n_1L)$ is the corresponding probability obtained in Model I; in which case, the population could be considered as distributed at the point $P_A(D/n_2L) = 1$. Equation XVI merely states that the measured probability for a particular value of a measurement is the mean probability for all the individuals who have that value of the measurement and the various values of other related measurements. In the limit as n_1 approaches infinity, $P_A(D/n_1L)$ approaches unity and $P(D/n_1L)$ is equal to the quantity in the bracket of equation XVI. Thus the intercept at $1/n_1 = 0$ is equal to the quantity in the bracket. Since these parameters are uncorrelated, the value of the bracket is the same for all values of n_1, and therefore we obtain these two curves with the same slope. Equation XII can be written as follows:

$$\text{(XII)} \qquad P(D/n_1\ , n_2L) = P_A(D/n_1L)\left[\sum^{n_2} \frac{N_L^{n_1 n_2}}{N_L^{n_1}} P_A(D/n_2L)\right] \cdot P_A(D/n_2L)\left[\sum^{n_1} \frac{N_L^{n_1 n_2}}{N_L^{n_2}} P_A(D/n_1L)\right]\left[\frac{1}{P(D/L)}\right]$$

In the special case where $P(D/n_1\ , n_2L) = 1$, then $P_A(D/n_1L) = P_A(D/n_2L) = 1$ and therefore:

$$\text{(XVII)} \qquad P(D/L) = \left[\sum^{n_2} \frac{N_L^{n_1 n_2}}{N_L^{n_1}} P_A(D/n_2L)\right]\left[\sum^{n_1} \frac{N_L^{n_1 n_2}}{N_L^{n_2}} P_A(D/n_1L)\right]$$

and obviously

$$\text{(XVIII)} \qquad P(D/n_1\ , n_2L) = P_A(D/n_1L)P_A(D/n_2L)$$

The closer a quantity within a bracket approaches unity, the less significant the parameter is in defining the population's death rate, and, conversely, as the value of the bracket approaches the death rate, the more important the parameter is in this respect. Also, as $P(D/n_1L)$ approaches unity when n_1 approaches infinity, the parameter becomes a more efficient predictor of mortality. It can be easily seen that if one bracket of equation XVII is unity, the other defines the death rate and, since each bracket is the other parameter's intercept, then the intercept of the one parameter is unity.

For a particular death rate versus age relationship, such as one finds for heart disease or cancer, the number of parameters and the magnitude of their possible relationship to the death rate are mutually dependent. The greater the number of non-intercorrelated parameters, the less their possible relationship to the death rate; that is, the less the slope of the curve of probability of death versus the value of the parameter. Therefore, if a disease has a multiple cause etiology, the problem of ferreting out the relationship becomes more difficult as the complexity of the disease process increases. In fact, the difficulty increases along a power series, since the probabilities are multiplicative. The foregoing has one important application. This is—having uncovered a relationship between a parameter and death rate from a

* See the Appendix for definition of the terms.

disease, one can assess the magnitude of the possible relationship of any further parameters. Equation XVI can be generalized to:

$$\text{(XIX)} \qquad P(D/n_1L) = P_A(D/n_1L) \prod^{n} \left[\sum^{n_x} \frac{N_L^{n_1 n_x}}{N_L^{n_1}} P_A(D/n_xL) \right]$$

As the $P(D/n_1L)$ approaches 1 when n_1 approaches infinity (α), the right hand term must also approach unity. Since, at the limit, $P_A(D/n_1L)$ is unity and none of the bracketed quantities may exceed unity, the only manner in which the product can go to unity is if each and every bracket goes to unity. Thus, the intercept on the probability axis at $n_1 = \alpha$ or $1/n_1 = 0$ is the minimum value that any remaining bracket may assume, or that the product of the remaining brackets may assume. The intercept can therefore be used to judge the relative efficiency of the parameter for predicting mortality, since, as the intercept approachs unity, its efficiency increases.

The above discussion applies primarily to non-intercorrelated parameters. With correlated parameters the value of the bracket will not be constant for all values of a parameter because, depending upon the correlation, the factor $N_L^{n_1 n_2}/N_L^{n_1}$ will change as the value of n_1 is changed. This will alter the slope of the curve of $P(D/n_1L)$ such that it will no longer be equal to the slope of the curve for $P_A(D/n_1L)$. As the degree of correlation increases, the slope will continue to change and the obtained curve will become more composite. At the point of perfect correlation, where $N_L^{n_1 n_2}/N_L^{n_1} = 1$, the following would apply:

$$\text{(XX)} \qquad P(D/n_1L) = P_A(D/n_1L)P_A(D/n_2L)$$

The association of any non-time-related parameters with death from a disease process will cause the curve of death rate versus time to approach a limit less than unity, as in Model II. This intercept on the death rate curve at $1/t = 0$ can therefore be of use in estimating the effectiveness of non-time related parameters in the disease death rate; it represents the maximum value of the intercept of any aging parameter in a plot of $P(D/n_1L)$ versus $1/n_1$, and also represents the product of all the brackets of equation XIX for the non-time-related parameters. If an aging parameter extrapolates to a death rate closely approximating the value of the intercept at $1/t = 0$, it can be considered as the primary aging process in the disease. If the bracket of a non-time dependent parameter approaches the value of this intercept, it can be considered as the primary non-time-dependent parameter associated with the death rate from the disease.

Equation XVII can be applied to Model II, in which there is one aging parameter and one non-time dependent parameter. The value of the bracket for the aging parameter will increase with age, since the population, with time, is distributed over higher values of the parameter which have larger probabilities of death. As a result, the intercept of the non-time-dependent variable will increase. Conversely, since individuals with larger values of the non-aging parameter die off at higher rates, the population will, in a relative sense, be distributed over lower values of this parameter, and its bracket will decrease in value as will the intercept of the aging parameter. In other words, as should be anticipated, the non-aging parameters become more important predictors of the death rate as the population's age increases, while the opposite applies to the aging parameter. This implies that the most efficient region in which to investigate an aging parameter lies in the younger age groups. The following consideration emphasizes this point, particularly so if a small population sample is used (and this is universally the case).

Given in figure 9 is a generalized probability curve of the type used in the models; but in this case the one axis is n instead of $1/n$. This curve, as is true of any prob-

ability curve, must have a limit not to exceed unity. Therefore, this curve approaches unity asymptotically. With time, the population will become distributed over larger values of the aging parameter and eventually could be distributed over the asymptotic portion of the curve. The difficulty in this case is obvious. It is not too unreasonable to assume that some population could distribute over this portion of the curve, in some aspect of a disease, while still in their teens. It may be that a population could be distributed over this portion of the curve on a number of related parameters, both aging and non-aging. In such a case the brackets of equation XVII for these parameters will be close to unity although the relationships to the death rate may be rather large. Thus the distribution can obscure a strong relationship since one can only measure that which exists in the population at the time of the study. This consideration should indicate the wisdom in choosing young populations for the study of aging processes.

Another significant comment about a probability curve of this general type is that an individual who lies in the asymptotic region of probability will have to effect a large change in the parameter before he enjoys any appreciable lowering of probability, while an individual lying in the steep portion of the curve can experience a large change in probability with only a modest lowering of the parameter. The foregoing can be summed up briefly by the statement: If a relationship between a parameter and the death rate from a disease can be demonstrated, it is conclusive evidence; however, if no relationship can be demonstrated, the result is not conclusive; particularly so if the sample is small and the population is at an advanced age.

The above considerations shall be summarized with respect to their effect on the two types of parameters. The non-time-dependent parameters will be considered first and then the aging parameters. It is important to point out again that, although these models may not find a place in reality, the information extracted from them is valid in reality.

NON-TIME-RELATED PARAMETERS

The curves of probability of dying at ages 30, 50, and 70 as a function of the non-time related parameter of Model II with $a = 200$ were given in figure 7. These curves have the same slope, but the intercept at $1/n = 1/150$ increases with increasing age. The ratio of the intercepts at two different ages is approximately equal to the ratio of the death rates for these ages. This will, in general, be true for a non-aging function; since its bracketed quantity of Equation XVII is essentially constant with age, its intercept, which is the other bracket of Equation XVII, must be the same fraction of the death rate at all ages. The value of the bracket does change somewhat with age due to a proportional increase in the distribution about lower values; but this should usually be small when compared to the increase in death rate with age.

In Model II the absolute probability of $n_2 = 150$ was set equal to unity. This means that the extrapolation of the curves in figure 7 beyond the point $1/n = 1/150$ is not correct. A horizontal line should connect this point with the probability axis. This model serves to indicate possible error which can be introduced by extrapolation beyond the points where data is available. In the absence of accessory information both the extrapolated point and highest point for which data is available could be used to place limits on the relationship. Of course the steepness of the slope of the curve will determine the probable error. As more information becomes available concerning the relationship of a parameter to the disease, a more critical estimate of the intercept can be made.

If, instead of this parameter, one which was correlated with it were measured, a curve of probability versus this new parameter could be obtained. If this new parameter has no relationship to the death rate except through the above correlation, then the slope of the obtained probability curves would approach, as a maximum,

the slope of the curves of figure 7 as the degree of correlation increased. The relationship of the ratio of the intercepts to the ratio of the death rates at different ages should not change, however, unless the degree of correlation changed with age. The value of the bracket of Equation XVII will be closer to unity for the correlated parameter than it would be for its correlative. If the two non-time-related parameters were correlated and each had an intrinsic relationship to the disease death rate, then the slope of the curves would be altered continually until the point of perfect correlation. With positive correlation the slopes would increase, with negative correlation they would decrease.

One rather critical feature of a non-time-related parameter is its ability to lower the intercept at infinite time. Thus the distribution of the parameter in the population, together with its relationship to the death rate, could place a limiting value on a population's rate of decay. This is done without altering the slope of the death rate curve as a function of age. Thus, if two populations existed which had different intercepts at infinite time, a difference in the distribution on a non-time related parameter should be suspected. It is these non-time-related parameters which determine the value of "*Do*" in the Gompertz function.

Lastly, since at any age individuals with higher values of the parameter are dying off at a greater rate, the mean value of a non-time-related parameter will decrease with age both in the living and dying population. This is the opposite to what occurs for the mean amount of accumulated aging.

AGING PARAMETERS

Aging parameters should be broken into two classes; one being parameters which are a measure of the rate of aging, and the other, those which are a measure of accumulated aging. This section will deal with the latter and the rate parameters will be considered in the succeeding section.

In the case of a disease which had only one associated aging process, the intercept of the aging parameter at $1/n = 0$ would be limited by the non-aging parameter and should be close to the value intercept at $1/t = 0$ on the death rate versus $1/t$ plot. The value of the intercept at $1/n = 0$ should decrease slightly with age since the product of the brackets of Equation XVII for the non-aging parameters should decrease with age. This is opposite to what occurs with a non-aging parameter.

If the parameter were merely correlated with the aging parameter and otherwise not associated with the disease, the slope of the probability curves at all ages would be lower. When the degree of correlation was low only the younger ages would demonstrate the relationship to the death rate and as the correlation increased it could be demonstrated at older and older ages. Thus at modest correlation the slope of the curve of probability versus $1/n$ would be gradually lowered with age until at an advanced age it would be zero. This occurs because as a population ages it becomes distributed over a more and more asymptotic portion of a curve such as that of figure 9 where low order correlation will be fuzzed out. Unless something bizarre occurs in a population, this situation of changing slopes with age should only occur in association with a correlation to an aging parameter. Such a bizarre occurrence would be a lowering with increasing age of the degree of correlation between two non-time-related parameters.

In the case of a disease which has more than one associated aging process, the intercept at $1/t = 0$ on the death rate versus $1/t$ curve is still the yardstick to use for estimating the effectiveness of the aging parameter in predicting morbidity. Equation XVII for a disease with two aging parameters would become:

$$[A]\ [B]\ [X] = P(D/L) \tag{XXI}$$

where $[A]$ and $[B]$ would represent the value of the brackets for the two aging parameters and $[X]$ the product of the brackets of the non-aging parameters which

is closely approximated by the intercept at $1/t = 0$ on the death rate versus $1/t$ curve. The intercept at $1/n = 0$ on the probability curve for the parameter of bracket A would be:

$$\begin{aligned} \textit{Intercept} &= [B]\,[X]\ , \\ \text{then} \quad [A] &= P(D/L)/[B]\,[X] \\ \text{and} \quad [B] &= \textit{Intercept}/[X] \end{aligned}$$

Since the value of the bracket for both aging parameters increases with age the ratio of the intercepts at $1/n = 0$ will rarely be equal to the ratio of the death rates between two ages. The ratio of the intercepts should generally fall between the square root of the ratio of death rates and unity. They would be equal to the square root of the ratio when both parameters remained equally effective but as one overtook the other in effectiveness the ratios for both parameters would approach unity. The measurement with the largest intercept at $1/n = 0$ would be the more strongly related measurement.

If these two aging parameters were intercorrelated the slopes of the probability curves would again change with age and depending upon the degree of correlation this effect would extend to older age groups. Low order correlations could be corrected from the younger ages by use of the curves at advanced ages where the effect of the correlation is fuzzed out and the slopes are less composite.

The mean amount of accumulated aging increases with age in both the living and dying population. This is in direct contrast to what occurs with non-aging parameters.

RATE PARAMETERS

The curves of probability of dying at various ages versus a rate parameter would appear similar to the curves of a parameter correlated with the amount of accumulated aging. That is, the slope of the curves would decrease with increasing age. It should be possible in most cases to distinguish between the two situations because in general the mean value of a rate parameter should decrease with age for the population of diers, while for a parameter correlated with the amount of accumulated aging, the mean should increase with age.

It is possible that the value of the rate parameter could increase in the population at such a rate as to cause mean value of the diers to increase with age. In such a case, however, the rate parameter would be highly correlated with the amount of accumulated aging and could be used in lieu of the aging parameter.

When an investigator is confronted with a rate parameter and lacks accessory information regarding the nature of the function:

Aging parameter $= \int_0^t f(\text{rate})\,dt$, there will generally be several alternatives open to him whether he chooses to be intuitive or forthright. For a rigorous extension, one would require the accessory information. However, a certain amount of pertinent data concerning the integrated function can be obtained from analysis with the rate parameter.

If a measurement of a rate parameter at some one age can be used to predict definitely the value of the rate parameter at all previous ages, then at any one age the rate parameter is perfectly correlated with the integrated aging function. The extrapolation of the probability curve for the rate parameter to $1/n = 0$ should lead to the same intercept as will extrapolation of the aging parameter. Furthermore at any one age the rate parameter would be equally as efficient a predictor of mortality as the aging parameter. The predictive ability of the rate parameter, at any one age, will depend upon degree of correlation between the rate parameter as measured at that age and the aging parameter. Both the slope and intercept of the probability curve derived from the rate parameter will decrease as the degree of correlation de-

creases. Therefore the value of the rate parameter's intercept at any age would represent a minimum value for the aging parameter's intercept.

There are some special considerations such as the possibility that the absolute probability of a measurement (Pa) need not extrapolate to unity at $1/n = 0$. These considerations will complicate the mathematics but will not alter the over-all considerations.

TREATMENT AND PREVENTION

An individual at age 55 will have a particular amount of accumulated aging and a particular rate of aging. The aging parameter together with the non-aging parameters will determine his probability of dying at that age; his rate of aging will determine his increment of probability at subsequent ages. On this basis one can calculate what his probability at age 65 will be. This calculated probability at age 65 could be reduced by one or a combination of the following three factors: (a) reduction of the value of non-time-related parameters, (b) reduction of the rate of aging, and (c) reduction of the present amount of accumulated aging. If the projected risk can be reduced, there should be no argument as to the possibility of accomplishing the reduction by either (a) or (b). Whether or not aging, once it is accumulated, can ever be regressed is a question of extreme moment from the standpoint of rational medical practice. The question is, "Can an individual grow substantially younger?" If the answer is yes then treatment of an aging process even at an advanced age could result in a substantial reduction in risk. If the answer is no then the logical approach is to keep people young by lowering their rate parameters early in life and maintaining them at a low level throughout the subsequent years.

The answer to this question would be of extreme importance to one who wished to design an experiment with the purpose of testing the efficacy of a therapeutic regimen by measuring mortality or morbidity changes. If the only effect possible was the reduction of the rate of aging, then it would be incumbent upon the investigator to use a young population and to allow a sufficient time for the difference in the rates to produce a sufficient difference in the aging parameter. This, unfortunately, is seldom the case in the experiments reported in the literature of the medical sciences. Even if the answer were yes, an amount of time would have to be allowed during which regression could take place. In any experiment involving aging, the time factor must not be overlooked. It is possible that some extremely useful remedies have been disregarded because of this oversight.

The ultimate answer to the question of regression will probably have to await a more complete understanding of the competing factor in the various diseases of aging. In the meanwhile, experiments conducted on these diseases should allow for either answer and for time.

SUMMARY

A method of evaluating physiological age was presented. The method is based upon an analysis of the association of biological measurements to death rates or to disease occurrence rates. This approach has the virtue of being quantitative and allowing the investigator to assess the relative importance of various measures to a disease process.

The requirements which must be imposed upon studies of aging processes were discussed. Primary among these was the necessity for controlling age and conducting the experiment on as many age groups as possible because not only the age-controlled information is important but also the age-dependent information.

The obvious necessity of accounting for time in any experimental study of an aging process was pointed out.

APPENDIX

Definition of Symbols:

$P(n_1/L)$ = Probability of having a particular value of parameter n_1 given being alive.

$P(n_1/D)$ = Probability of having a particular value of parameter n_1 given having died within the previous year.

$P(D/L)$ = Probability of dying within one year given being alive.

$P(n_2/n_1L)$ = Probability of having a particular value of parameter n_2 given having a particular value of n_1 and being alive.

$N_L^{n_1}$ = Number of individuals alive with a particular value of parameter n_1.

$N_D^{n_1}$ = Number of individuals who die in one year and have a particular value of n_1.

N_L^T = Total number of individuals living.

N_D^T = Total number of individuals who die in one year.

$N_L^{n_1n_2}$ = Number of individuals alive with a particular set of values for the two parameters n_1 and n_2.

$N_D^{n_1n_2}$ = Number who die in one year and have a particular set of values for the two parameters n_1 and n_2.

$\sum^{n_1}$ = This notation means that one must sum over all value of the measurement n_1.

Since by definition

I. $$P(n_1/L) = \frac{N_L^{n_1}}{N_L^T}; \qquad P(n_1/D) = \frac{N_D^{n_1}}{N_D^T}; \qquad P(D/L) = \frac{N_D^T}{N_L^T}$$

then

II. $$P(D/n_1L) = \frac{N_D^{n_1}}{N_L^{n_1}} = \frac{P(n_1/D)}{P(n_1/L)}P(D/L)$$ = Equation XI of the text

and

III. $$P(D/n_2L) = \frac{P(n_2/D)}{P(n_2/L)}P(D/L)$$

IV. $$N_L^{n_1n_2} = N_L^{n_1}[P(n_2/n_1L)] \quad \text{since} \quad P(n_2/n_1L) = \frac{N_L^{n_1n_2}}{N_L^{n_1}}$$

If n_1 and n_2 are completely independent then:

V. $$P(n_2/n_1L) = P(n_2/L) \quad \text{and thus}$$

VI. $$N_L^{n_1n_2} = N_L^{n_1}[P(n_2/L)] = N_L^T[P(n_1/L)][P(n_2/L)]$$

and similarly

VII. $$N_D^{n_1n_2} = N_D^T[P(n_1/D)][P(n_2/D)]$$

Thus by Equation II, III, VI, and VII

VIII. $$P(D/n_1n_1L) = \frac{N_D^{n_1n_2}}{N_L^{n_1n_2}} = \frac{P(D/n_1L)P(D/n_2L)}{P(D/L)}$$

and in the general case Equation VIII becomes Equation XI of the text. If the parameters are correlated, Equation V does not hold, and Equation IV must be applied. Then the Equation for correlated parameters is:

$$\text{IX.} \qquad P(D/n_1n_2L) = P(D/n_1L)\,\frac{P(n_2/n_1D)}{P(n_2/n_1L)}$$

and in the general case Equation IX becomes Equation XIII of the text.

ADDENDUM

Aging and Coronary Artery Disease

The choice of coronary artery disease as an example for the study of aging is by no means purely academic. A long-standing clinical impression (like old wives' tales they often have a basis in fact) is, "Man is only as old as his arteries." One of the salient features of coronary artery disease is atherosclerosis, the deposition of lipids in the walls of the arteries. Numerous pathological studies (3, 6, 7) have demonstrated that this is a chronic accumulative disease rather than an acute process. These studies show that the average degree of atherosclerosis increases in the population with age and that those dying with clinically manifest signs of the disease have, on the average, a greater degree of involvement of the coronary arteries with the atherosclerotic process. The nature of this relationship of atherosclerosis with coronary artery disease is sufficient to suggest that this process is an important, if not the sole, aging process associated with deaths resulting from coronary artery disease. Furthermore the degree of atherosclerosis in the coronary vascular bed correlates to a considerable extent with the degree in other vascular beds (9). In general this process of deposition of fat in the arteries of the body has been given as a prime factor in the course of a great number of the ills which befall human beings as they advance in age (5).

After accepting this eminently reasonable hypothesis as an approach to the pathogenesis of coronary artery disease, the next logical step would be to ascertain the extent to which the degree of atherosclerosis in the coronary bed was predictive of mortality from coronary artery disease. It is not feasible to measure directly the degree of atherosclerosis in the coronary vascular bed of a living individual, and therefore the investigator is forced to search for a biological measurement which is strongly correlated with the direct measurement and can be performed on a living population. Again the straightforward method of determining this correlation is to make the indirect measurement on a living population, wait for the population to die, and then make the direct measurement. This attack could prove to be very costly in time, particularly if a number of uncorrelated measurements were investigated before a strongly correlated measure was uncovered.

A more practical approach is to use the group of individuals in the population who have developed clinical manifestations of the disease as a test medium for the biological measurements. As a group, these individuals should have an average degree of atherosclerosis which is higher than that for the remainder of the population. It should be pointed out at this time that regardless of the approach which leads to the correlations, or the interpretations made of them once they have been found, the correlations found between biological measurements in these two groups shall be able to stand on their own merits. A measurement which is able to predict the morbidity or mortality of coronary artery disease does it regardless of or in spite of any interpretation of its role in the disease.

It was probably this association of atherosclerosis with coronary artery disease which has long suggested that the disease is somehow related to certain lipid constituents of the body. In particular evidence has accumulated (2) which demonstrates a strong relationship between coronary artery disease and the concentration of certain serum lipoproteins.

Given in table 2 are the means and standard deviations of the concentration of S_f° 0-400 lipoproteins in the serum for males by decades between the ages of 40 and 60 years. Listed are the values for a group of individuals who have survived a myocardial infarction and a group who show no clinical evidence of coronary artery disease together with the results of the usual "t" test for significance of the difference between means.

Listed in table 3 are the mean values for rate of aging and the mean amount of aging accumulated by the individuals who remain alive and those who die at various ages. These data are from Model I ($K = 24{,}000$) of the previous section. It will be noted that, whereas the mean amount of accumulated aging among those who die at any age increases with age, the mean rate of aging decreases. Furthermore, as table 1 shows, the mean value of the S_f° 0-400 lipoprotein concentration decreases with age among the myocardial infarction groups. This would indicate that if a relationship between the lipoproteins and an aging process in coronary disease exists it must be due to a correlation with the rate of aging rather than to the amount of accumulated aging.

At this point the situation has developed where a rate parameter has been uncovered but accessory information regarding the nature of the rate equation is lacking. However, as mentioned earlier, a certain amount of pertinent data concerning the integrated function $\int(\text{rate})\,dt$ can be obtained from analysis with the rate parameter.

If a measurement of a rate parameter at some one age can be used to predict definitely the value of the rate parameter at all previous ages, then at any one age the rate parameter is perfectly correlated with the integrated aging function. The extrapolation of the probability curve for the rate parameter to $1/n = 0$ should lead to the same intercept as would extrapolation of the aging parameter. Furthermore at any one age the rate parameter would be equally as efficient a predictor of mortality

as the aging parameter. The predictive ability of the rate parameter, *at any one age*, will depend upon degree of correlation between the rate parameter as measured at that age and the aging parameter. Both the slope and intercept of the probability curve derived from the rate parameter will decrease as the degree of correlation decreases. Therefore the value of the rate parameter's intercept at any age would represent a minimum value for the aging parameter.

The curves of probability of dying as a function of the concentration of S_f^o 0-400 lipoproteins for the age groups listed in table 2 are given in figure 10. The probabilities were calculated using Equation XI. The intercepts at $1/n = 0$ in figure 10 are not the same at all ages. This would suggest that either the concentration of S_f^o 0-400 lipoproteins are poorly correlated with the aging parameter or that more than one aging parameter was involved in the disease. An analysis of the intercepts at $1/n = 0$ in figure 10 indicates that the bracket of equation XVII for the lipoproteins (which is calculated by dividing the death rate from figure 2 by the appropriate intercept of figure 10) lies between the square root and the cube root of the death rate for the respective age group. This means that the lipoproteins have a predictive efficiency between $\frac{1}{3}$ and $\frac{1}{2}$ or that there is most likely no more than two other aging parameters which are equally as predictive unless they are correlated with the lipoproteins.

On the other hand if we undertake the same analysis without extrapolating the data beyond the region where data exist, it develops that the lipoproteins have a predictive efficiency of approximately $\frac{1}{5}$ or that there could be no more than 4 other aging parameters which are equally as predictive. The data for these analyses are presented to table 4. The figures in the column labeled "Power of Death Rate" are the predictive efficiencies. The relative constancy of these Powers would indicate that there is probably little contribution from non-time-dependent variables in heart disease. As the predictive ability of a parameter decreases these powers should approach zero. Since with increasing age, it should be anticipated that non-time-related parameters would increase in predictive ability, then it should be expected that these powers would decrease for aging parameters in diseases associated with non-aging parameters. The extrapolation of the curve in figure 2 to unity was already cited as possible evidence for a lack of non-time dependent variables in heart disease. There, of course, are alternate hypotheses to this fact. One could postulate that there is a synergistic effect between the non-time-dependent variable and the aging variables. In such a case a non-time-dependent parameter would appear similar to an aging parameter. Its mean, however, would not increase with age and this could be used to separate it from the aging parameter.

It is the information contained in figure 10 and in table 4 that we attempt to glean from ordinary statistical procedures. It would seem that much of this information is lost by the process of condensing the data into a few statistical numbers. A set of tables which would relate the ordinary statistical numbers such as the "*t*" test, chi square, and biserial correlation coefficient to this type of information would be extremely helpful.

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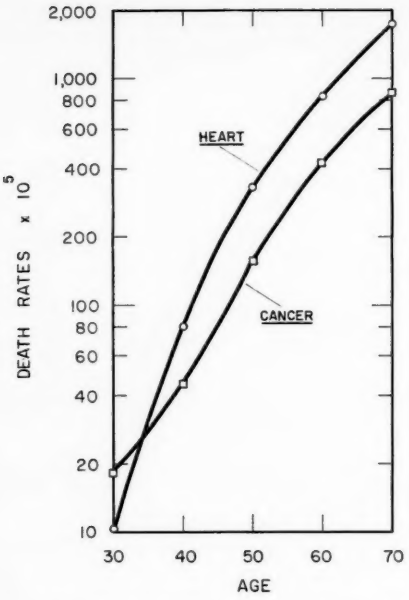

Fig. 1. Death rates for cancer and heart disease (rates versus age on a semilog scale). These are for white males and were taken from *U.S. Vital Statistics*, 1954, Vol. I. Cancer includes classifications 140-205; heart is for arteriosclerotic heart disease, category No. 420.

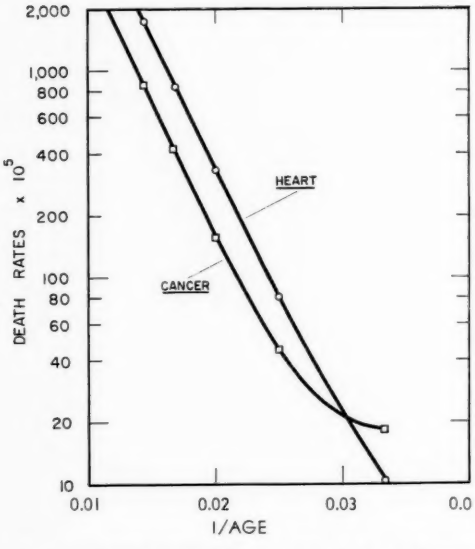

Fig. 2. Death rates for cancer and heart disease (rates versus 1/age on a semilog scale).

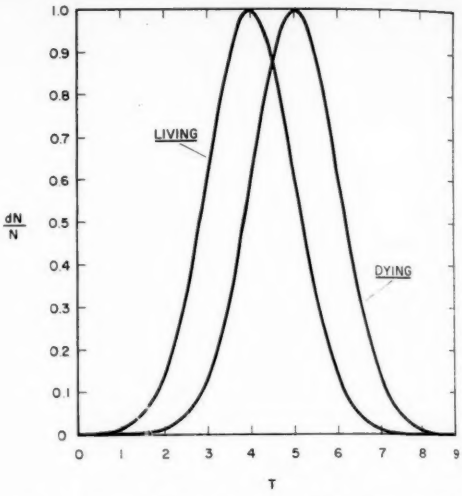

Fig. 3. Normalized distribution of the function "*T*" for an imaginary living population and for those who will die within one year.

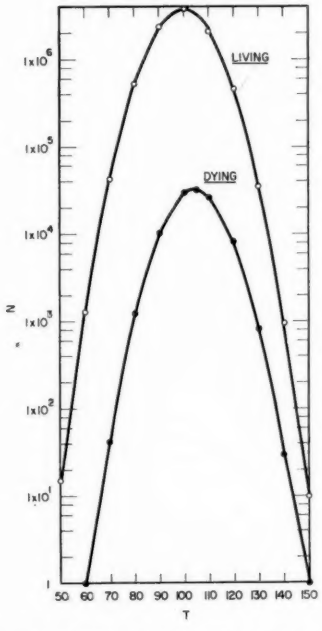

Fig. 4. Distribution of the function "*T*" for an imaginary living population and for those who will die within one year.

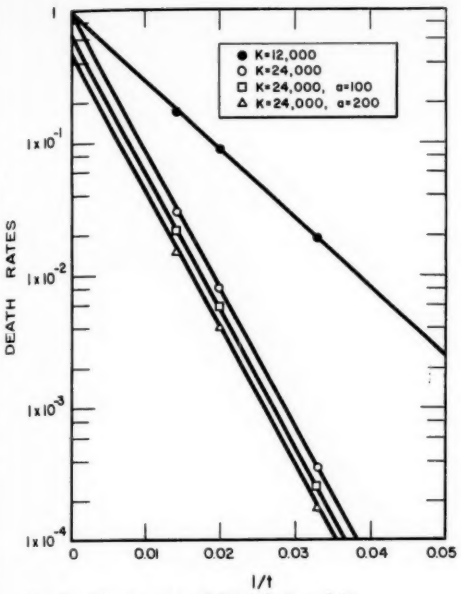

Fig. 5. Death rates of Models I and II.

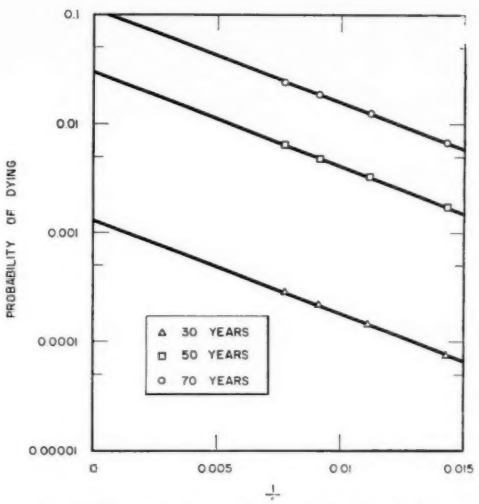

Fig. 7. Probability of dying as a function of the non-time related parameters of Model II ($a = 200$).

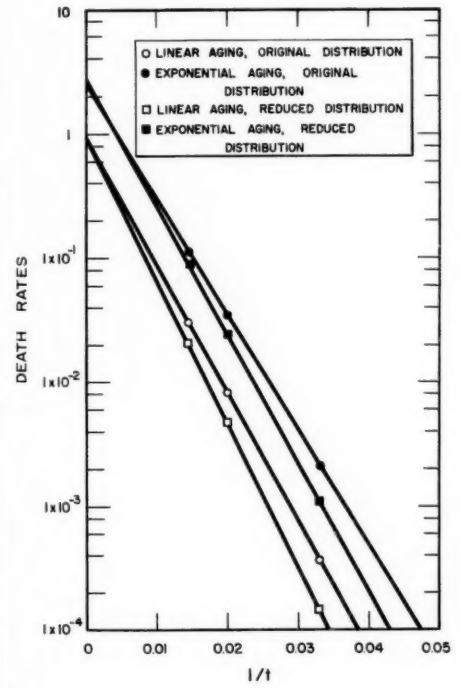

Fig. 6. Death rates of Models III and IV.

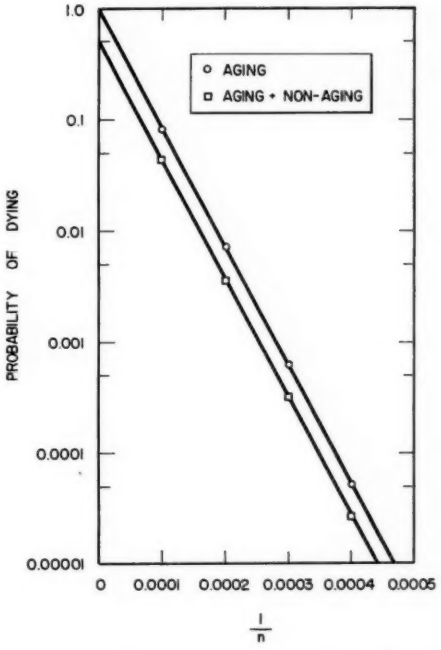

Fig. 8. Probability of dying as a function of an aging parameter ($k = 24{,}000$), with and without a non-aging parameter.

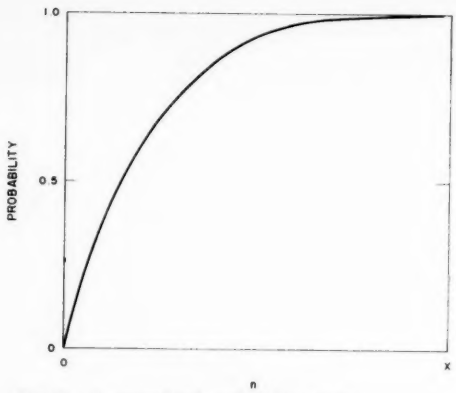

Fig. 9. A generalized probability curve.

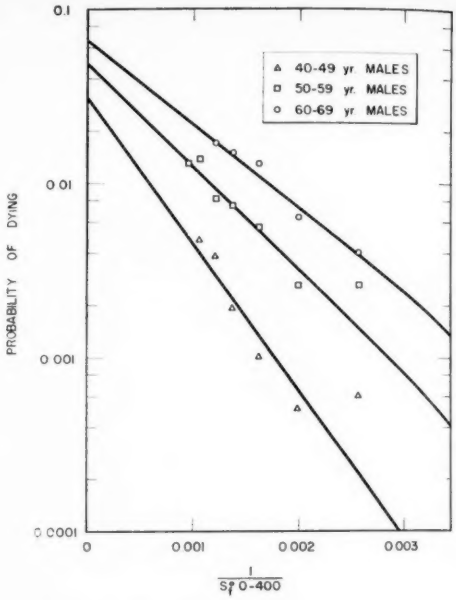

Fig. 10. Probability of dying as a function of S_f (0-400) lipoproteins.

TABLE 1. PERCENTAGE OF PEOPLE ALIVE AT VARIOUS AGES

Age	Linear Aging		Exponential Aging	
	Original Rates	10% Reduced Rates	Original Rates	10% Reduced Rates
30	99.9	99.9	99.2	99.6
50	93.4	96.3	72.7	81.3
70	63.7	74.7	15.9	25.4

TABLE 2. S_f^0 0-400 SERUM LIPOPROTEIN CONCENTRATIONS FOR MALES BY DECADES.

Myocardial Infarction Survivors				Group with No Clinical Evidence of Coronary Disease				
N	Mean Age	S_f^0 0-400 Concentration (Mg.%)		N	Mean Age	S_f^0 0-400 Concentration (Mg.%)		t Test Significance
		Mean	Standard Deviation			Mean	Standard Deviation	
113	45.4	746.1	181.0	1817	44.2	619.4	172.9	0.01
210	54.9	698.2	163.5	1416	54.3	622.5	165.8	0.01
144	63.9	672.9	164.6	402	62.6	609.5	159.3	0.01

TABLE 3. MEAN RATE AND $\int$ RATE DT VALUES FOR ABSTRACT POPULATIONS (MODEL I, K = 24,000)

Age	Diers		Survivors	
	Mean Rate	Mean $\int$ Rate dt	Mean Rate	Mean $\int$ Rate dt
30	107.2	3216	100.0	3000
50	104.2	5210	99.7	4985
70	101.6	7112	98.7	6909

TABLE 4. ANALYSIS OF INTERCEPTS.

Decade	Death Rate	Data		Extrapolation		Power of Death Rate	
		Intercept	Bracket	Intercept	Bracket	Data	Extrapolation
40-49	.0015	.006	.25	.027	.055	.20	.44
50-59	.0055	.015	.38	.054	.10	19	.44
60-69	.01	.020	.50	.072	.14	.15	.43

MATERNAL AGE SELECTION AND THE FERTILITY OF MICE

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(From the Biological Station of Roswell Park Memorial Institute, Springville, New York)

Fertility of mammals is known to be a highly variable characteristic which has been shown to be greatly influenced by endocrinologic, radiologic, and chemical treatments. Fertility may also be influenced greatly by hybridization, thus indicating a genetic influence. However, a survey of the literature has demonstrated that little or no work has been done on the effect of the aging of the mother on fertility (total number of offspring of her progeny). When Strong discovered a difference in susceptibility to chemically induced fibrosarcomas between mice of early litters and late litters (7), the lack of information concerning other characteristics that might be similarly affected prompted the development of a stock of mice selected by maternal age.

We have previously reported (10) that the mice of 6 maternal age descents derived from a single outcross of mice of two inbred strains show differences in the ages at the time of birth of their first litters. Thus it was demonstrated that the different independent sublines have different parabola curves when their successive means of age of first litters (on a generation basis) are compared to the general mean of first litters for the entire population (73.04 days).

In the present paper it is proposed to report on the fertility of the same females as reported in the previous study on the ages of first litters (10).

MATERIALS AND METHODS

The 826 mice used in this experiment were of the Strong Polydactylia strain. The history of these mice has previously been reported by Strong and Hardy (8), and by Engel (3). The observations described here, with the exception of the New Haven F_1 series, were made on animals housed at the Biological Station in Springville under conditions outlined by Kreitner (4) and described more completely by Strong (6).

The breeding pattern of this strain was reported by Strong and Fuller (10). However, a brief outline of this procedure is included here. The F_1 generation of a cross between a polydactylous mutant male belonging to the Brpb strain (a NHO subline) and females of the C_{57} strain were divided into groups by the age of their mothers at the time of their births. The offspring, which were born within the time period designated by the mother's classification, were continued by brother-sister matings exclusively: normal by normal for two generations and poly by poly for all subsequent generations. Studies on the fertility (total number of offspring produced) of these mice are reported here.

RESULTS

The number of offspring produced by the 826 females of the F_1-F_4 inbred generations were recorded and analyzed. The mean numbers of offspring for the indicated 5 maternal age classes are given in table 1. The differences among these means were tested by the modified analysis of variance test described by Welch (11).

Table 2 gives the standard deviation of the observations within the indicated classes. The significance of the differences among the descent variances in each generation was tested by the modification of Bartlett's test for homogeneity of variances described by Box and Anderson (1). The difference which is significant at the 99% confidence level (F_1 Springville) is indicated by an asterisk.

Figure 1 is the graph of a function we have termed the quotient Q. It is given the formula $Q = S/\bar{s}$ where S is the sample standard deviation and $\bar{s}$ is the pooled estimate of the standard deviations. This function Q reduces the normal variability for each generation to $Q = 1$. Thus the changes in variability are shown relatively independent of the changes due to inbreeding.

DISCUSSION

The most obvious difference in fertility of mice was encountered between the two F_1 series—the one at New Haven, the other in Springville. This is difficult to explain on any basis other than that the physical conditions of the Springville laboratory may have been better for mice. The same food for the mice

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* This experiment has been made possible, in part, by a grant (H2666) from the National Heart Institute of the National Institutes of Health, United States Department of Health, Education, and Welfare.

TABLE 1. MEAN TOTAL OF OFFSPRING FOR FEMALE MICE FOR THE FIVE MATERNAL AGE DESCENTS OF THE FIRST FOUR GENERATIONS OF INBREEDING.

	< 100		101-200		201-300		301-400		401-500		Pooled	
	F†	N†	F†	N†	F†	N†	F†	N†	F†	N†	F†	N†
F_1 New Haven	78.85	33	66.86	70	60.39	41	43.33	9			66.32*	153
F_1 Springville	90.00	24	87.24	21	85.48	59	87.63	79	76.09	11	86.63	194
F_2	56.80	10	48.15	46	54.96	56	59.67	36	51.75	8	53.99	156
F_3	70.41	17	61.76	49	55.38	34	50.55	44	54.00	3	57.77*	147
F_4	53.60	15	51.07	70	51.93	45	54.95	43	57.33	12	52.79	185

* Significant at the 99% confidence level.
† F indicates fertility, i. e., mean total number of offspring; N indicates the number of females in each determination of number of offspring produced.

(Nurishmix, manufactured by the Pratt Food Co.) was used in both places. The three differences between the mice of the two series were: 1) the laboratory at New Haven was air-conditioned, making it difficult to eliminate airborne diseases, whereas the one at Springville was not; 2) the different water supply; and 3) in New Haven the sexes were continued together until the female failed to produce a litter for 60 days, whereas in Springville the sexes were continued together until one of them died. Very few females ever have a new litter with a litter spacing of more than 60 days so that it is believed that the difference in fertility between the two series cannot be due to this practice.

The data at present are not sufficient to make the final analyses of the various influences, genetic and otherwise, bearing upon the fertility of mice. This can only be done after the various maternal age descents have reached a greater degree of inbreeding and perhaps crossings between mice of two or more descents. Thus it is hoped that the relative influence of hetergeneity, homogeneity, etc., can be resolved. However, sufficient information is now available on 826 breeding females to indicate trends. At least the partial analysis of the biological nature of fertility between the F_1 and the F_4 generations of inbreeding should be recorded.

A significant difference of fertility among the females of the five maternal age descents was encountered in the F_1 New Haven series and in the F_3 generation housed at Springville. There is evidence that differences exist in the other generations also, but these differences are numerically small and cannot be conclusively demonstrated by an experiment of this size. Females of the <100 day class showed a consistently higher number of offspring than the pooled value for each generation.

Tests for homogeneity of variances disclosed that a significant difference between the females of the different maternal age descents occurred only in the F_1 Springville series. However, the data from the <100 day and 101-200

TABLE 2. STANDARD DEVIATIONS OF DATA PRESENTED IN TABLE 1 BY THE MODIFIED METHOD OF BARTLETT.

	< 100	101-200	201-300	301-400	401-500	Pooled
F_1 New Haven	22.18	26.37	28.89	35.23	——	26.80
F_1 Springville	32.86	26.91	18.83	21.05	28.16	23.48*
F_2	20.86	24.79	21.70	24.29	30.52	23.67
F_3	21.14	21.43	23.91	26.27	44.71	23.99
F_4	22.02	24.11	26.40	29.24	24.15	25.81

* Significant at the 99% level.

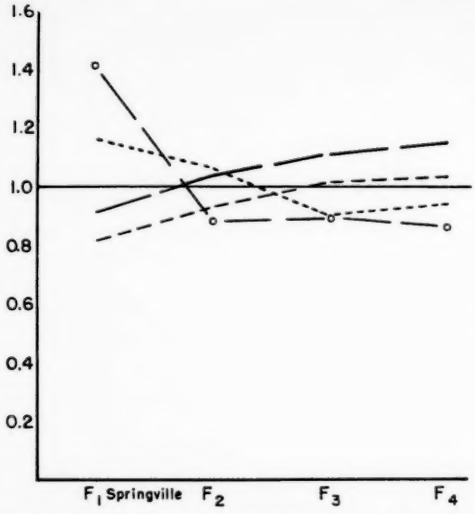

Fig. 1. Quotients of variation (Y-axis) plotted against the generation of inbreeding (X-axis) for the 4 descents. The pooled sample for the entire population is on the solid line; the data for the <100 day maternal age descent are on the solid dot and long dash line curve; for the 101-200 day class on the short dash line; for the 201-300 day class on the intermediate dash line; and for the 300-400 day class on the long dash line.

day descents tend to decrease between F_1 and F_4 whereas similar data for the 201-300 day and 301-400 days descents tend to increase during the same generations of inbreeding. That is, it appears that the homogeneity of females in relation to fertility is either becoming stabilized or showing a possible reversed tendency.

Tendencies for variations to occur counter to the trend of selection have been discussed by Lerner (5), Dobzhansky (2), and Strong (9). Dobzhansky (2) referred to homeostasis as a "gift of natural selection." Natural selection, however, is a slow process and our findings seem to show that the average fertility of mice may be immediately influenced within a few generations; but not greatly impaired by maternal age selection alone. The variability among animals within the same descent obviously follows a definite pattern. A two-way F-test of variances disclosed that the increased variability of the 201-300 day descents and 301-400 day descents and the decreased variability of the <100 day descent was significant at the 95% confidence level.

These observations correspond very well with our findings on the age of first litters (10). The mean age of first litters showed a small but significant difference in the F_1-F_4 generations combined. In the F_5-F_8 generations the differences were so small that they were not significant despite the pooling of data. However, the animals in the several descents showed a decided difference in variability.

SUMMARY

A statistical analysis of observations concerning the fertility of 826 mice belonging to 5 maternal age descents derived from a single outcross of a polydactylous mutant male to several C_{57} females is reported for the first 4 generations of inbreeding. Possible inferences to a homeostatic mechanism or a system of biological equilibrium is discussed with reference to fertility and previously reported data on the age of first litters. It is interesting that the mean value of fertility for females of the five independent descents do not differ significantly but that the coefficients of variability for the females of the separate descents of inbreeding do.

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POST-TRAUMATIC VARIATIONS IN PHOSPHATASE AND RESPIRATORY ENZYME ACTIVITIES OF THE PERIOSTEUM OF AGING RATS

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Studies involving alkaline phosphatase localization and activity have been made of a number of animals in the past by numerous investigators in normal developing and growing bone, in fractures, and several pathological conditions (1, 4, 5, 6, 11, 16, 19, 22, 23, 24, 26, 28, 29, 31). Acid phosphatase activity, however, has been only slightly investigated in bone and periosteum (20, 28, 29). The relationship of parathyroid to bone and acid phosphatase was studied by Kochakian (15). More recently, Schajowicz and Cabrini (25) have shown large quantities of acid phosphatase in osteoclasts and chondroclasts in rat bone. These authors consider a role of acid phosphatase in bone resorption mechanisms. Previous investigations (28, 29) on the alkaline and acid phosphatase activity of the periosteum of rats from birth to old age have indicated that both these enzymes are in abundance throughout the life of the animal and become somewhat elevated at the period of maximum rate of bone growth.

With the development of histochemical methods for the demonstration of respiratory enzyme activity, Follis (10) and Follis and Berthrong (13) revealed the presence of cytochrome oxidase and succinic dehydrogenase in fresh hand-cut slices of bone and cartilage. Tonna (27, 28, 29) reported respiratory enzyme activity changes in normal periosteum of rats at various ages. Cytochrome oxidase and succinic dehydrogenase activities also seemed elevated at a period which represented higher phosphatase activities. The respiratory enzymes, however, fell drastically and remained at a very low level throughout the following life span of the animal.

The present investigation is a continuation of the above-mentioned work, which has been extended to the comparative variations of phosphatase and respiratory enzyme activities following trauma and the possible significance of these variations to bone growth and repair with increasing age.

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Grateful acknowledgment is made to Miss N. Pillsbury for her technical assistance.

MATERIALS AND METHODS

One hundred rats of the Long-Evans strain were segregated into 5 age groups. Each group was made up of 10 males and 10 females. Group I consisted of 1-week-old, Group II of 5-weeks-old, Group III of 8-weeks-old, Group IV of 26-weeks-old, and Group V of rats ranging between the ages of 65 to 104 weeks.

Both femora from each animal were drilled in the midshaft portion with a dentist's drill (fig. 1). Group I and II were sacrificed one week post-operatively, while the rats of the subsequent age groups were sacrificed two weeks following surgery. Immediately after death, cross sections or shavings were taken from the traumatized mid-diaphyseal region of one leg and fixed in 80% alcohol, chilled acetone, and 10% formalin fixative, respectively. Frozen sections were also prepared and studied immediately for respiratory enzymes. X-rays were taken of the opposite femur.

The fixed tissues were treated routinely and were examined for activities of acid phosphatase, alkaline phosphatase, cytochrome oxidase, and succinic dehydrogenase, as described in a previous publication (29). The semiquantitation of the results was based on visual inspection of the intensity of the precipitate or staining reaction; the findings were compared with those recorded in a previous study (29) on 1-week-old, non-traumatized rats. The observations for this age group of normal animals was used as the base line for the comparisons.

RESULTS

Alkaline and acid phosphatase. At the site of trauma alkaline and acid phosphatase activity was seen to be elevated throughout all the age groups studied. This activity seemed greatest along the developing tissue fibers of

the fibrous and osteogenic layers of the periosteum growing into the traumatized area (fig. 2). The cellular components of the periosteum and callus also exhibited intense activities. This was especially true of the osteoblasts and osteogenic cells in the immediate area of repair. At times the alkaline phosphatase activity was so high that the abundance of black precipitate made histological observation impossible. The periosteal areas which were not affected by the injury revealed the same phosphatase distribution and activities as were found in non-traumatized animals and reported previously (28, 29).

Respiratory enzymes. The findings of the respiratory enzyme activity following trauma were quite different from those found for the phosphatases. Cytochrome oxidase and succinic dehydrogenase activity patterns paralleled each other. The variations noted, however, were more pronounced for succinic dehydrogenase

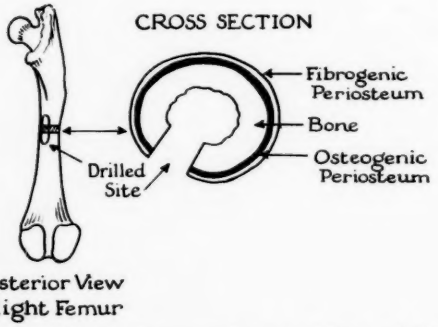

Fig. 1. A diagrammatic representation of a rat femur and the region drilled in the experiments accompanied by a corresponding tissue cross section.

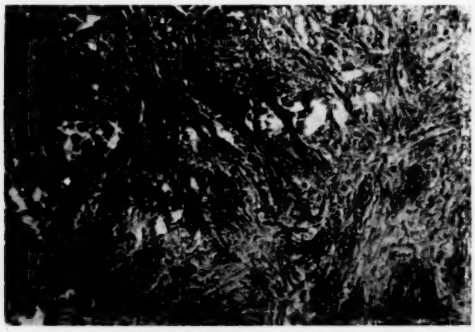

Fig. 2. Cross section of a femur at the trauma site of a 1-week post-operative 5 weeks-old rat. The photomicrograph reveals abundant proliferation of periosteal fibrous connective tissue growing into the traumatized area. The fibers and cells exhibit intense alkaline phosphatase activity. Gomori method. X 50.

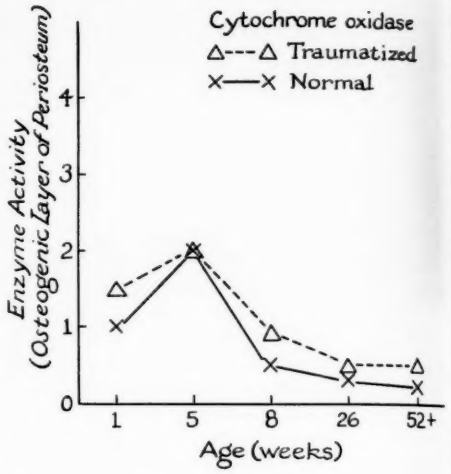

Fig. 3. A comparison between the distribution of cytochrome oxidase in the osteogenic layer of the mid-femoral region of the periosteum of normal and traumatized rats at different ages. The enzyme activity is based on the visual inspection of the sections and comparison of the intensity of the blue staining. Some increase in enzyme activity is associated with trauma to the bone. However, this is not noted at about the age of maximum rate of bone growth.

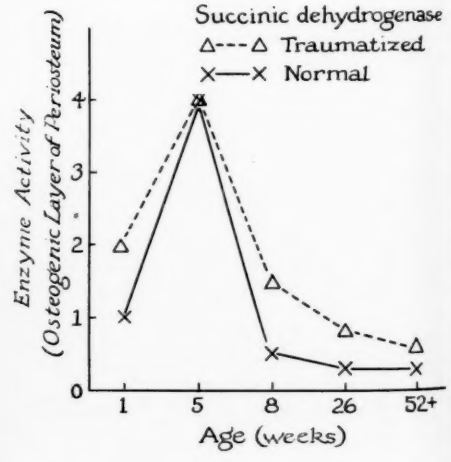

Fig. 4. A comparison between the distribution of succinic dehydrogenase in the osteogenic layer of the mid-femoral region of the periosteum of normal and traumatized rats of different ages. The enzyme activity is based on the visual inspection and comparison of the intensity of purple formazan crystals. The pattern is similar to that of cytochrome oxidase; however, it is more dramatic.

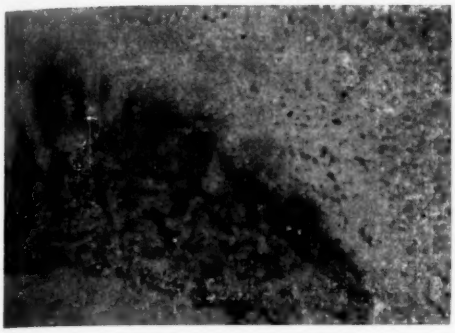

Fig. 5. A cross section of the femur taken from a 5-weeks-old rat, 1 week after trauma. Intracytoplasmic formazan crystals indicative of succinic dehydrogenase activity can be seen scattered throughout the noncounterstained tissues. Increased activity is noted in the osteogenic layer of the periosteum at the surface of bone seen in the left lower half of the photomicrograph. The periphery of the trauma callus exhibits the greatest activity. Straus, Cheronie and Straus method. X 50.

(fig. 3 and 4), than for cytochrome oxidase.

In 1-week-old animals an elevation in respiratory enzyme activity was noted about the whole area of trauma but was especially concentrated at the outermost edges of the callus closest to the diaphysis (fig. 5). All the cells appearing at the trauma site revealed the presence of blue granules in the cytoplasm indicative of cytochrome oxidase activity and intracytoplasmic purple formazan crystals indicative of succinic dehydrogenase activity. Numerous formazan crystals were also seen in the osteogenic cells of the callus. The increase in the activity of the respiratory enzymes in the 1-week-old traumatized rats did not, however, reach the high level previously reported (28, 29) for 5-weeks-old non-traumatized rats. The rats in age groups II to V likewise showed an

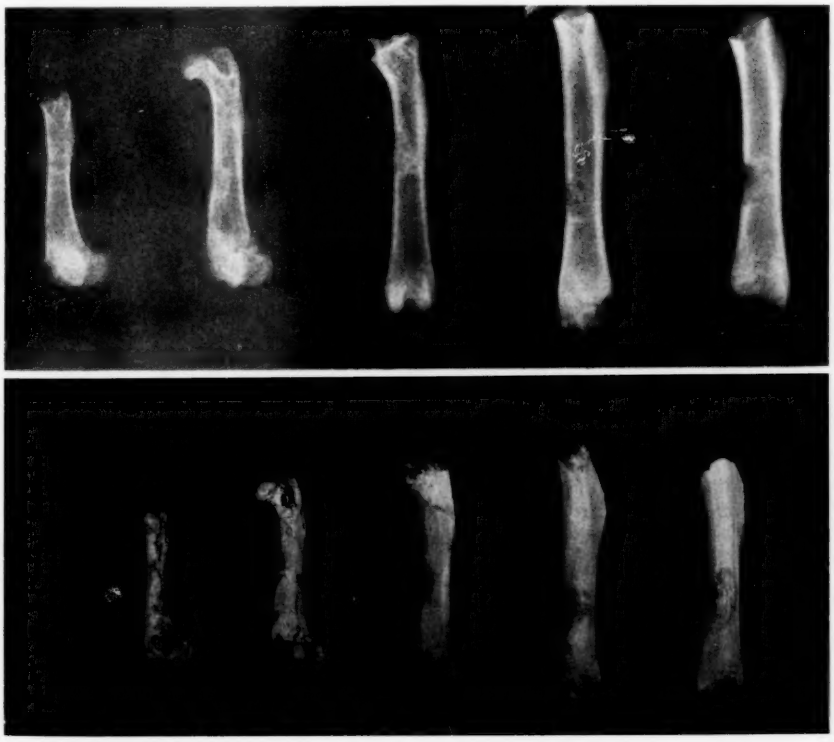

Fig. 6. A gross and x-ray comparison of the extent of femoral repair with increasing age. The post-operative (P.O.) time the specimens were examined is also included. Note with increasing age the reduced rate of repair of the defect.

increase in respiratory enzyme activity following traumatization; with increasing age, however, the stimulated respiratory enzyme response became progressively less.

Gross studies. Examination of the gross femora revealed a slower repair of traumatized bone with increasing age. This was further substantiated by the x-ray examination, which showed that at 1 and 5 weeks of age the injured cortex was almost completely repaired within one week after injury, whereas, in the older groups the processes of repair were still active two weeks after injury. In the oldest animals, at the end of two weeks, the edges of the injured cortex were still noticeable (fig. 6).

DISCUSSION

Previous investigations by the present author (28, 29) have shown that an abundant alkaline phosphatase activity of the periosteum of normal rats is maintained throughout the life of the animal. Bourne (4, 5) indicated that upon aging an increase in dephosphorylating enzyme activities was noted in 16 tissues studied; bone, which may represent a different situation than other tissues with regard to such enzyme functions was, however, not investigated. It has also been shown by Bourne (2, 3, 6) that within 24 hours alkaline phosphatase activity was intense in the periosteum around traumatized areas of the femora and the skull of guinea pigs. Masses of phosphatase-positive fibers were noted in the repair areas, as late as two weeks after injury. Periosteal cells appeared positive within 48 hours after injury and were found to remain so until repair was complete (19). Similar observations were made in the present investigation on rats, i.e., alkaline phosphatase activity was elevated at the site of injury, especially along the fibers. It is of interest to point out that this is also true with regard to acid phosphatase and that throughout the age of the animal (1-104 weeks) both phosphatases increased upon injury to the bone.

The role of alkaline phosphatase in the formation of bone matrix has been accepted by many investigators (7, 12, 17, 18, 24). It seems possible, as has been pointed out previously (28), that acid phosphatase shares a role with alkaline phosphatase in the processes of bone growth, development, and repair. The appearance of abundant quantities of phosphatases upon injury throughout the life of the animal indicates that as far as the formation of bone matrix necessary for bone healing is concerned, the presence of these enzymes is assured even in old animals. It seems likely, therefore, that other factors, which may possibly be related to the activities of respiratory enzymes, are responsible for the longer periods required for complete bone healing in aging animals. Thus 1) the amount of protein collagen necessary for bone matrix formation may be produced at a slower rate; 2) the proper molecular orientation of the protein fibers may have been changed so as to alter the normal stages leading to calcification; and 3) the tissue mucopolysaccharides, which are believed by some investigators to act as a bond between collagen and the mineral phase of the bone, may have been altered.

It was suggested in the previous studies (28, 29) that factors other than phosphatases are involved in bone repair. Various investigators (8, 9, 14, 21) have demonstrated that the number of mitochondria is reduced in inactive cells and in osteocytes. Studies on mitochondrial changes in aging rats, carried out by the present author (30), have revealed a reduction in the number of mitochondria per osteoblast from an average of 38 at 5 weeks to 4 at the age of 104 weeks. It seems likely that such mitochondrial changes may involve the activities of the respiratory enzymes and of the oxidative-phosphorylative mechanism of the cells, the latter supplying the essential energy to drive cellular reactions. In the present study, an increased activity of the respiratory enzymes, succinic dehydrogenase, and cytochrome oxidase, was observed at the site of trauma. With increasing age, however, the ability of the respiratory enzymes to become stimulated following trauma was seen to lessen, but some increase in over-all respiratory activity following trauma was noted even in the oldest animals. The failure to observe a post-traumatic increase in respiratory enzyme activity in the 5-weeks-old rats (Group II) is taken to indicate that the cells at this age level are respiring at a maximum or near maximum rate.

It is believed by the author that a reduced respiratory enzyme activity with increasing age is indicative of reduced oxidative-phosphorylative activity of the mitochondria resulting in a reduction or alteration in the production of the substances necessary for bone repair.

SUMMARY

Histochemical studies were made including alkaline and acid phosphatase, cytochrome oxi-

dase, and succinic dehydrogenase activities of the periosteum in the traumatized femora of 100 Long Evans strain rats from 1 to 104 weeks of age. Both alkaline and acid phosphatase activity increased to high levels following trauma in all ages studied. This phosphatase activity appeared generally in all the cells and fibers involved at the trauma site. Cytochrome oxidase and succinic dehydrogenase activity also increased after trauma except at the age of maximum bone formation. This is believed to indicate that the cells involved with repair at this time are already operating at a maximum or near maximum rate. With advancing age, the increase in activity of respiratory enzymes following trauma became progressively less.

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THE AGE FACTOR IN THE PRODUCTION OF VARIOUS EXPERIMENTAL CARDIOPATHIES

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In various animal species it is possible to elicit an electrolyte-steroid-cardiopathy with necroses (ESCN) by combined treatment with certain corticoids and Na-salts (1). In the course of our studies in this field, we noted incidentally that the production of such lesions is much easier in old than in young animals. Since, in man, the incidence of cardiac lesions is likewise greatly increased with the progress of age, we decided to examine the role of the age factor in the production of various experimental cardiopathies which more or less closely imitate certain spontaneous myocardial changes of man.

The histologic characteristics of these experimental cardiopathies have been described in detail elsewhere (1). Let us merely point out here that we employed as pathogens: 1) papain, because this proteolytic enzyme preparation elicits acute, miliary, disseminated myocardial necroses; 2) plasmocid (a rather toxic, and now obsolete, antimalarial) since it produces large, patchy myocardial necroses and myocarditic lesions that are singularly resistant to the various corticoids and electrolytes which influence many other types of experimental cardiopathies; 3) noradrenaline and vasopressin, as agents capable of producing "spotty myolysis," with disappearance of muscle-fiber segments, without extensive necroses or inflammation; 4) stressor agents, such as forced restraint or quadriplegia induced by a transection of the motor nerves of all 4 extremities, which likewise produce only "spotty myolysis," (in animals not specially sensitized by corticoids or Na-salts); 5) dihydrotachysterol, a steroid of the vitamin-D group, because it causes intense calcium deposition in the heart and in the coronary arteries; 6) 2α-methyl-9α-chlorocortisol (Me-Cl-COL) + NaH_2PO_4, since this combined corticoid-electrolyte treatment is highly effective in producing a typical ESCN, characterized by massive, infarct-like cardiac necroses, with secondary inflammation, but without any demonstrable histologic change in the structure of the coronary arteries. We believed that such a wide variety of potentially cardiotoxic agents, given to immature, adult, and old rats, would give us a fair indication of the type of cardiac lesion that is significantly influenced by age.

MATERIALS AND METHODS

Two hundred forty female rats, of the Sprague-Dawley strain (purchased from the R. Roubidoux Farm, St-Constant, Quebec), were subdivided into 24 groups of 10. The approximate age of the animals was as follows: 4 weeks (50 Gm.), 45 days (100 Gm.), and

TABLE 1. THE AGE FACTOR IN THE PRODUCTION OF VARIOUS EXPERIMENTAL CARDIOPATHES.

Group	Treatment	Body Weight (Gm.)	Cardiac Lesions	Mortality (%)
1	Papain	50	0.2 ± 0.17	10
2	Papain	100	0.9 ± 0.27	0
3	Papain	300	2.6 ± 0.23	90
4	Plasmocid	50	1.2 ± 0.49	40
5	Plasmocid	100	1.8 ± 0.25	80
6	Plasmocid	300	1.4 ± 0.38	40
7	Noradrenaline	50	0.2 ± 0.15	0
8	Noradrenaline	100	0.7 ± 0.15	0
9	Noradrenaline	300	1.6 ± 0.23	0
10	Vasopressin	50	0	0
11	Vasopressin	100	0.4 ± 0.17	0
12	Vasopressin	300	1.3 ± 0.20	0
13	Restraint	50	0	0
14	Restraint	100	0.5 ± 0.28	0
15	Restraint	300	0.3 ± 0.17	0
16	Quadriplegia	50	0.2 ± 0.20	0
17	Quadriplegia	100	0.2 ± 0.17	0
18	Quadriplegia	300	0.2 ± 0.15	0
19	Dihydrotachysterol	50	0.3 ± 0.15	10
20	Dihydrotachysterol	100	1.8 ± 0.32	10
21	Dihydrotachysterol	300	2.0 ± 0.27	10
22	Me-Cl-COL + Na_2HPO_4	50	0	0
23	Me-Cl-COL + Na_2HPO_4	100	0.6 ± 0.23	0
24	Me-Cl-COL + Na_2HPO_4	300	1.6 ± 0.30	70

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10 months (300 Gm.). Each of the 8 potentially cardiotoxic agents used in this study was tested, under otherwise identical conditions.

Papain is a proteolytic enzyme contained in the dried latex of *Carica papaya*. Five Gm. of crude papain powder (Fisher Scientific Co., Limited) were added to 50 ml. of distilled water; this turbid suspension was mixed in a Waring blendor for 10 minutes and then passed through a No. 40 Whatman filter paper; 0.2 ml./100 Gm. body weight of the resulting clear, amber-colored filtrate was injected into the jugular vein, under light ether anesthesia, once on the first day. All the surviving rats were killed 48 hours following the papain injection.

Plasmocid (8-(3-diethylaminopropylamino)-6-methoxyquinoline, The Lilly Research Laboratories) was given at the dose of 0.4 mg./100 Gm. body weight, always in 0.2 ml. of water, intraperitoneally, three times on the first day. The experiment was terminated 48 hours following the last injection.

Noradrenaline (Sterling-Winthrop Institute) was given twice daily, at the dose of 250 μg/100 Gm. body weight, in 0.2 ml. of oil, subcutaneously, during the first two days. The rats were killed on the fourth day of the experiment.

Vasopressin (Parke, Davis and Co.) was injected during the first and second days, at the dose of 10 I.U./100 Gm. body weight, in 1 ml. of water, twice daily, subcutaneously. The animals were killed 48 hours following the last treatment.

Restraint was applied, on the first day of the experiment, by strapping the rats with adhesive tape to a wooden board, in the prone position, for 17 hours. During this time, the animals struggled in an effort to free themselves and hence were under considerable stress. All animals were killed 48 hours after the initiation of the restraint.

Quadriplegia, through motor denervation of the extremities, was performed on the first day, under ether anesthesia. Both cervical plexuses, as well as the femoral, obturator, and sciatic nerves, were severed. The experiment was terminated on the second day following the operation.

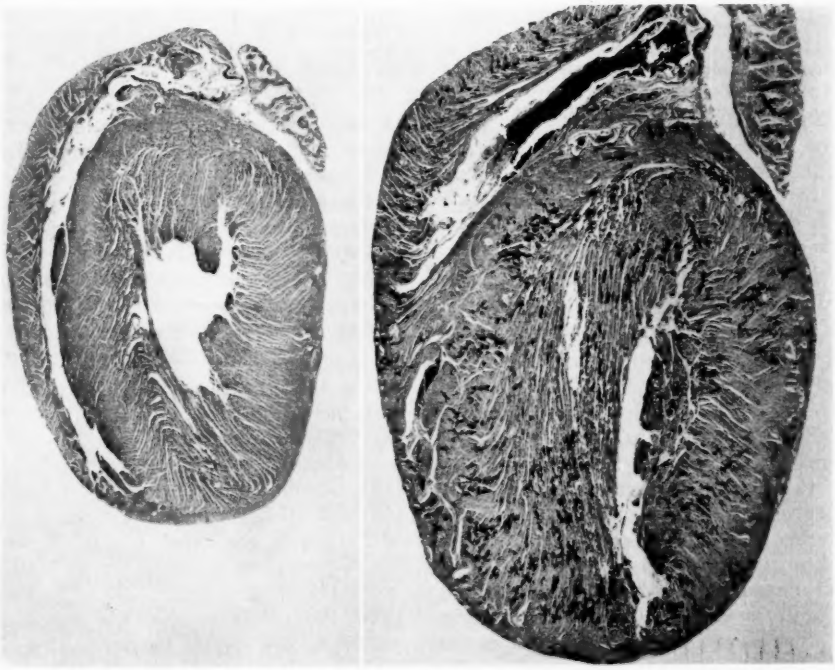

Fig. 1. Cross-section through the whole heart of a 50 Gm. (left) and a 300 Gm. rat of Groups 19 and 21, respectively. Note complete absence of calcium deposition in the heart of the young animals, while that of the old rat is studded with calcified (here black) tissue lesions (von Kossa X 11).

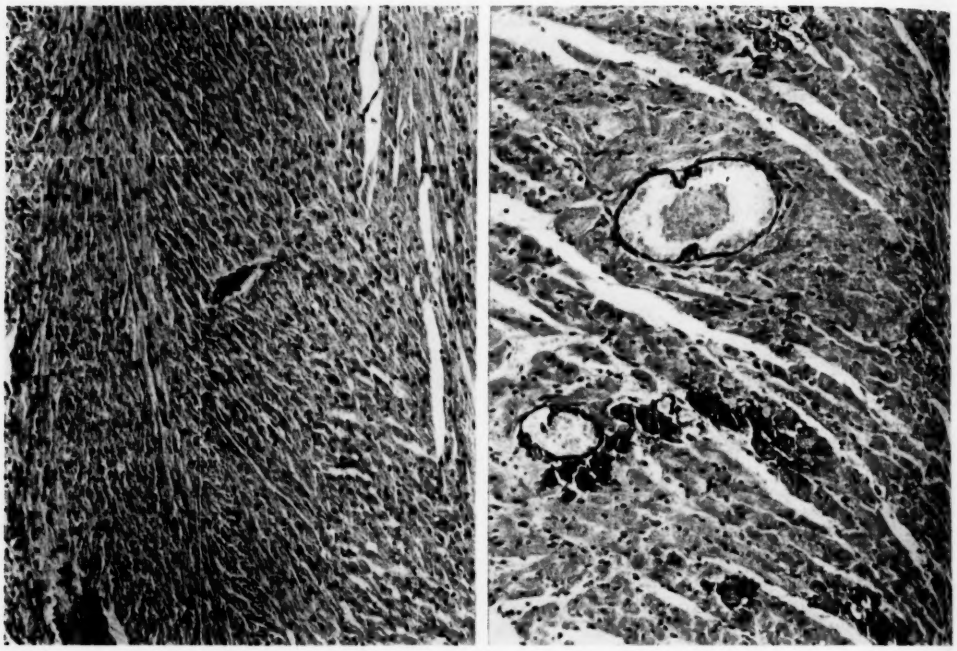

Fig. 2. Higher magnification of comparable regions from the hearts of the rats shown in figure 1. There is no detectable change in the myocardium of the young rat (left), while, in the older animal (right), there is intense calcification in myocardial fibers, as well as in the walls of the coronaries (von Kossa X 120).

Dihydrotachysterol (Dr. A. Wander, A.G.) was given in the form of a microcrystal suspension, at the daily dose of 300 μg/100 Gm. body weight, in 0.5 ml. of water, by stomach tube, during 5 days. The rats were then killed on the sixth day.

Me-Cl-COL (2α-methyl-9α-chlorocortisol, The Upjohn Company) was injected subcutaneously, in the form of microcrystals of its acetate, at the daily dose of 100 μg/100 Gm. body weight, during 5 days.

Na_2HPO_4 ("dibasic sodium phosphate, Reagent," Fisher Scientific Co., Limited) was administered at the dose of 1 mM/100 Gm. body weight, twice daily, in 2 ml. (the amount of 3 mM, however, in 4 ml.) of water, by stomach tube, during 5 days. The experiment was terminated on the sixth day.

In all instances, the hearts were first inspected with the aid of a dissecting loup, immediately after autopsy, and then fixed in neutral formalin for subsequent embedding in paraffin. The sections were stained with von Kossa's technique for the histochemical demonstration of calcium (using a hematoxylin-phloxine counterstain), because several of the cardio-toxic agents produce calcium depositions in the heart. The severity of the lesions was assessed in an arbitrary scale of 0-3, depending upon the intensity of the cardiac lesions (necrosis, inflammation, calcification). In table 1 we list the means of these determinations (with standard errors), as well as the percentual mortality rate of each group.

RESULTS

It is evident, from the data in table 1, that, with increasing age (and size), the cardiotoxic effect of several among the agents used becomes more severe. These agents are: papain (Groups 1-3), noradrenaline (Groups 7-9), vasopressin (Groups 10-12), dihydrotachysterol (Groups 19-21), and combined treatment with the ESCN-producing combination of Me-Cl-COL + Na_2HPO_4 (Groups 22-24). On the other hand, the age factor does not appear to play any important role in the production of myocardial lesions by plasmocid (Groups 4-6), restraint (Groups 13-15), or quadriplegia (Groups 16-18).

Histologic study of the hearts essentially con-

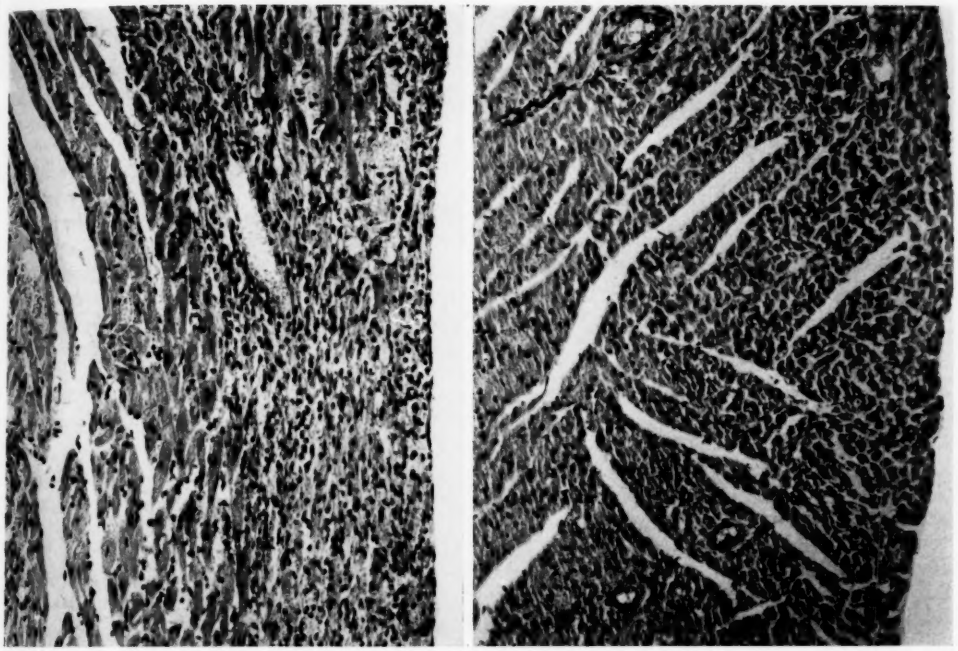

Fig. 3. Subendocardial layer of the ventricles from a 50 Gm. (left) and a 300 Gm. (right) rat of Groups 22 and 24, respectively, that were treated with Me-Cl-COL + Na_2HPO_4. The myocardium of the young rat exhibits no structural anomaly, while there are intense necroses, with secondary inflammation and connective-tissue proliferation underneath the endocardium of the older animal. This localization of the lesion and the comparative scarcity of calcium deposits (in this region there are none) are characteristic of the ESCN (von Kossa X 120).

firmed earlier data concerning the types of cardiac lesions produced by the agents that we employed (1). In the case of stimuli with age-dependent cardiotoxic activity, the quality of the structural alterations was not especially dependent upon age; the lesions were merely more intense in the older animals and occasionally absent in the young ones (figs. 1-3).

DISCUSSION

It is not yet clear why the cardiotoxic effect of some agents is, while that of others is not, dependent upon age. As mentioned in our introduction, the myocardial lesions produced by the means we employed differ widely in their structural characteristics. For example, papain produced predominantly acute, disseminated necroses, dihydrotachysterol calcification in the heart and its arteries, while noradrenaline and vasopressin induced "spotty myolysis." However, the histologic lesions elicited by restraint or quadriplegia were rather similar to those evoked by noradrenaline or vasopressin, and yet the action of the latter hormones was evidently dependent upon age, while that of restraint and quadriplegia was not.

Of course, the dose of the hormones (as well as that of all other drugs) was adjusted in proportion to the body weight; hence, the older rats, with a mean body weight of 300 Gm., received 6 times as much as the young animals, which weighed only 50 Gm.; no such adjustment was possible (or deemed necessary) in the event of restraint or quadriplegia.

It is also possible that the cardiotoxicity of restraint and quadriplegia was too mild to serve as a test object for this type of study. Nonspecific stressors, such as these, notoriously produce massive, infarct-like myocardial necroses only following "conditioning" with steroids or, better, with steroids and Na-salts (1).

However, neither of these explanations is applicable to the results obtained by plasmocid. This drug produced a very definite cardiac lesion at the smallest dose level in the young rats that weighed 50 Gm. but a 6 times higher dose was no more effective in the old animals

whose body weight was 300 Gm. Essentially the same may be said about the mortality rates. The lethal effect of plasmocid seemed to be independent of the absolute dosage employed, while the other cardiotoxic agents that produced any mortality caused the greatest number of deaths among the oldest rats. In connection with the exceptional behavior of plasmocid it may be mentioned that, unlike most other agents that produce extensive myocardial necroses and myocarditis, treatment with plasmocid is also singularly irresponsive to aggravation by corticoids and Na-salts, or to prophylaxis by KCl and $MgCl_2$.

With our present-day methods, it may be difficult to verify the cause of these apparent discrepancies and to identify the specific mechanisms through which age influences the susceptibility of the myocardium to the production of morphologic lesions. Five of the 6 chemical agents that we used to produce myocardial lesions were significantly more effective in large than in small rats. Yet we have no proof that this difference is due to age rather than size. On the other hand, restraint and quadriplegia —which naturally could not be adjusted to body weight—were about equally effective in young and in old rats. Still, in view of the enormous importance of cardiovascular disease in gerontology, it is of interest that a variety of experimental cardiac lesions depends so largely upon the age factor.

SUMMARY

Experiments on 240 female rats, 4 weeks to 10 months of age, were performed to examine the importance of the age factor in the production of various experimental cardiac lesions, which differ widely from each other, both as regards their causative agents and their histologic characteristics.

It was found that papain, noradrenaline, vasopressin, dihydrotachysterol, and combined treatment with 2α-methyl-9α-chlorocortisol (Me-Cl-COL) + Na_2HPO_4 induce much more pronounced cardiac lesions in old than in young rats, when the dose of these substances is adjusted to body weight. On the other hand, under the same circumstances, plasmocid is essentially equally effective in producing cardiac lesions in young and old animals.

Two highly stressful procedures, which did not depend upon the injection of exogenous drugs or hormones (forced restraint and motor denervation of all 4 extremities) produced only mild and inconstant cardiac lesions, irrespective of the age of the experimental animals.

The role of the age factor in the pathogenesis of spontaneous and experimental cardiovascular disease is briefly discussed on the basis of these observations.

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THE EFFECT OF BREED, AGE, AND SEX ON MYOCARDIAL NECROSIS PRODUCED BY ISOPROTERENOL IN THE RAT

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In a recent publication (2) we have described the production of infarct-like myocardial necrosis in the rat by isoproterenol (1-(3,4-dihydroxyphenyl)-2-isopropyl amino ethanol hydrochloride) (Isuprel®). It was shown (12), using a wide range of doses of this drug subcutaneously, that the severity of the lesion was directly proportional to dosage, so that lesions of predictable severity could be produced. These reports were the first disclosures of infarct-like myocardial changes after the administration of a synthetic adrenergic agent. It was shown further (3), that in this respect isoproterenol is more potent that l-epinephrine or l-arterenol when compared on the basis of the respective toxic doses or absolute amounts.

The organic lesions which we have observed in the rat after isoproterenol treatment were not mentioned in the toxicity studies of Dertinger and associates (7) and Lands and associates (9). These authors found no significant gross or histopathological abnormalities in the rat after the daily administration of 100 mg./kg. of this compound subcutaneously for 15 days. In an attempt to reconcile our findings with those of the authors mentioned above, we have studied factors such as strain, age, weight, and sex which may have influenced our results.

MATERIALS AND METHODS

The rats used in this study were housed under controlled conditions of temperature and humidity and fed a commercial rat food. Four groups of 10 animals were used to study the influence of breed differences. One group was hooded animals of the Long-Evans strain, one group was albino rats of the Sprague-Dawley strain, the remaining two groups were albino rats of the Wistar strain from two different inbred colonies. The groups were composed of 5 males and 5 females. The average weight of the animals of the various groups was similar (216-238 Gm.)

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To study the influence of age, weight, and sex, 8 groups of 25 Wistar rats were used. The average ages and weights of the female groups were 2½ weeks, 47 ± 0.4 Gm.; 6 weeks, 120 ± 1.4 Gm.; and 16 weeks, 241 ± 1.7 Gm.; and those of the male groups 2½ weeks, 57 ± 1.2 Gm.; 4 weeks, 103 ± 2.1 Gm.; 6 weeks, 216 ± 3.5 Gm.; 10 weeks, 307 ± 2.2 Gm.; and 16 weeks, 386 ± 3.3 Gm., respectively. The animals were chosen so as to be comparable in terms of age. We intentionally used relatively young animals to avoid vascular factors and other cardiac diseases present in old rats (13). Since the females are always smaller at a given age, a strict correlation cannot be drawn from the same groups on a weight basis. From each group 5 rats served as controls and the remaining animals were treated.

Isoproterenol was given subcutaneously as the hydrochloride of the racemic mixture on two consecutive days. Two doses were chosen, 72.6 mg./kg. and 4.5 mg./kg. in terms of the base. The larger dose was found to be most effective in producing infarct-like myocardial necrosis and the smaller dose is the minimal dose necessary to produce regressive changes in the heart muscle (12). Control animals received distilled water. Forty-eight hours after the first injection the rats were killed and an autopsy performed. The hearts were removed, weighed, and the gross lesions were graded according to a system which we described in detail elsewhere (12) and which may be summarized as followed:

Grade 0: no lesions. Grade 1: mottling of the apex and distal parts of the left ventricle caused by intermingled pale and dark red streaks. Grade 2: well demarcated necrotic areas limited to the apex. Grade 3: large infarct-like necrosis involving at least one-third of the left ventricle and extending to adjacent areas of the interventricular septum and right ventricle. Grade 4: large infarct-like necrosis involving more than half of the left ventricle, the inter-

ventricular septum and extending to the distal portion of the right ventricle.

After fixation in Bouin's fluid frontal sections of the heart, which included both atria, ventricles, and interventricular septum, were embedded in paraffin. Sections cut at 5μ were stained with hematoxylin-eosin, Cason's trichrome (1) and P.A.S. (11). Frozen sections of the heart were stained with Sudan IV. Microscopically, the hearts were graded as follows: Grade 0: no lesions, Grade 1: focal lesions of the subendocardial portion of the apex and/or the papillary muscle composed of fibroblastic swelling or proliferation and accumulation of histiocytes. Grade 2: focal lesions extending over wider areas of the left ventricle with right ventricular involvement, lesions included edema, mottled staining, fragmentation and segmentation of muscle fibers. Grade 3: confluent lesions of the apex and papillary muscles with focal lesions involving other areas of the ventricles and the atria. The lesions included vacuolar and fatty degeneration, granular disintegration, and hyaline necrosis of the muscle fibers. Marked capillary dilation was present with hemorrhages, pronounced mononuclear cell and leukocytic infiltration. Extensive edema, occasionally with a mucoid component, caused sequestration of muscle fibers. Grade 4: Confluent lesions throughout the heart including infarct-like massive necrosis with occasionally acute aneurysm or mural thrombi. The infarcts were usually apical, but also occurred in the papillary muscles or the right ventricle. The histologic lesions were similar in character to those in grade 3. Histological sections were also made of other organs in which gross pathologic conditions were observed, and in two additional animals from each group sections were made of the brain, lung, liver, and kidney.

RESULTS

The results of the administration of isoproterenol to various strains of rats are shown in table 1. At a dose of 72.6 mg./kg. administered on two consecutive days there was mortality in from 0 to 20% of the animals. In all the groups heart enlargement and marked gross and microscopic cardiac necrosis were seen. The average severity of the gross cardiac lesion varied from grade 2.1 to grade 3.6, and that of the microscopic changes from grade 3.1 to grade 4.0.

The results of the study on the influence of body weight on the severity of the myocardial lesions are presented in table 2. Both male and female rats treated at the high or low dose levels of isoproterenol developed gross and microscopic myocardial lesions irrespective of their body weight. However, it will be noted that the severity of these lesions is directly related to age or body weight. Lesions of the greatest severity were found in the male and female animals treated at 72.6 mg./kg. (fig. 1). Gross and microscopic lesions of lesser severity were found in all other treated animals with the exception of those treated at 4-5 mg./kg. Three of the female animals treated at this dose did not have lesions visible in the gross, and in two of these no microscopic lesions were found. The corresponding male group contained 4 animals without gross lesions, and 2 of these were free of changes when examined histologically.

When the severity of the lesions in the male and female groups is compared no significant differences are found if the comparison is made between groups of equal body weight. However,

TABLE 1. ACTIVITY OF ISOPROTERENOL IN PRODUCING CARDIAC LESIONS IN VARIOUS STRAINS OF RATS WHEN ADMINISTERED SUBCUTANEOUSLY ON TWO CONSECUTIVE DAYS AT 72 MG./KG. DAILY.

Groups	Mean Body Weight (Gm.)	Mean Heart Weight Mg./100 Gm. Body Weight	Number of Rats	Mortality	Average Grade of Heart Lesion	
					Gross	Microscopic
Wistar (Colony A)	233 ± 5.2	573 ± 21	10	1	3.6	4.0
Wistar (Colony B)	216 ± 12	517 ± 27	10	0	3.0	3.5
Sprague Dawley	224 ± 3.5	526 ± 21	10	0	2.1	3.1
Hooded L.E.	238 ± 3.2	590 ± 17	10	2	3.2	3.5

TABLE 2. INFLUENCE OF AGE, WEIGHT, AND SEX ON THE SEVERITY OF CARDIAC LESIONS PRODUCED BY ISOPROTERENOL.

Sex	Dose (Mg./Kg.*)	Age (Weeks)	Body Weight (Gm.)	Heart Weight Mg./100 Gm. Body Weight	Mortality	Average Grade of Heart Lesion	
						Gross	Microscopic
Female	4.5	2.5	46 ± 1.2	763 ± 15	0	0.8	1.0
"	"	6	120 ± 2.2	734 ± 38	0	1.5	1.8
"	"	16	238 ± 3.3	406 ± 15	1	1.6	2.1
"	72.6	2 5	46 ± 1.0	736 ± 15	0	1.5	1 5
"	"	6	120 ± 2.6	589 ± 19	0	1.9	2.2
"	"	16	234 ± 3.6	470 ± 22	0	2.5	3.2
"	Control	2.5	48 ± 1.4	632 ± 10	0	0	0
"	"	6	121 ± 6	537 ± 20	0	0	0
"	"	16	251 ± 6	345 ± 11	0	0	0
Male	4.5	2.5	56 ± 1.8	749 ± 30	0	0.7	1.0
"	"	4	48 ± 2.5	638 ± 18	0	1.4	1.8
"	"	6	198 ± 3.8	533 ± 21	0	2.1	2.4
"	"	10	298 ± 4.4	475 ± 25	0	2.5	3.1
"	"	16	380 ± 2.3	418 ± 14	3	2.4	2.8
"	72.6	2.5	64 ± 1.4	737 ± 26	0	1.5	1.5
"	"	4	112 ± 3.0	603 ± 31	1	1.7	2.0
"	"	6	221 ± 8.2	513 ± 26	0	3.3	3.4
"	"	10	305 ± 4.7	492 ± 14	4	3.7	3.9
"	"	16	398 ± 3.9	—	7	3.9	3.9
"	Control	2.5	52 ± 1.2	573 ± 27	0	0	0
"	"	4	91 ± 2.6	467 ± 20	0	0	0
"	"	6	228 ± 8	394 ± 8	0	0	0
"	"	10	316 ± 5.1	364 ± 12	0	0	0
"	"	16	389 ± 4.0	326 ± 17	0	0	0

* Daily dose administered on two consecutive days.

Fig. 1. Hearts from male Wistar rats weighed an average of 208 Gm. Those on the upper line were treated with 72.6 mg./kg. isoproterenol on 2 consecutive days; those on the lower line are saline controls. Severe infarct-like myocardial necrosis is present in all treated animals.

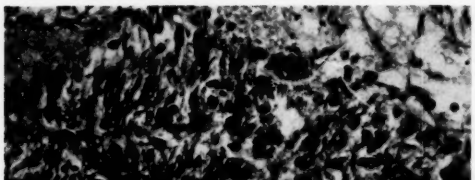

Fig. 2. Hyaline necrosis of the heart muscle surrounded by inflammatory reaction. Rat treated with isoproterenol hydrochloride 72.6 mg./kg. subcutaneously on 2 consecutive days. P.A.S. x 300.

when groups of equal age are compared a greater severity is noted in the male groups. The apparent greater susceptibility of the male animals can therefore be attributed to their faster rate of growth and greater weight at any given age compared to the females.

The histological lesions in the male and female animals of 50-120 Gm. treated at either the high or low dose were focal and composed of interstitial edema, histiocytic infiltration, fibroblastic swelling, and proliferation. Larger animals of both sexes revealed confluent or massive infarct-like cardiac necrosis. The regressive changes of the myocardial fibres predominated and the most characteristic lesion was hyaline necrosis (fig. 2). The involved fibers became homogenous, strongly eosinophilic, P.A.S. positive, and stained deep red with Cason's trichrome. Striation of the muscle fibers was lost, and the nuclei were either shrunken or had disappeared. Around the necrotic areas leukocytic-histiocytic infiltration, edema and fibroblastic changes developed. In pronounced cases edema of the mucinous type separated the muscle fibers. No evidence of coronary arterial changes was seen in any of the animals.

Table 2 indicates that the heart weight/body weight relationship of normal rats decreases with age and increase in body weight. The same is true for the rats treated with isoproterenol. Within the groups of similar body weight and sex the isoproterenol treatment at either a high or low dose causes heart enlargement, which was significant at the 95% level of confidence in 14 of the 16 groups studied. The greater sensitivity of larger animals to isoproterenol treatment is reflected in the mortality rate in the various groups. The greatest number of deaths was 7 in the 16-weeks-old male group, given the highest dose level. No deaths occurred in the female group of the same age receiving the same dose of isoproterenol.

Apart from focal and mild fibrosis observed in the heart of one large male, the control rats revealed no gross or microscopic abnormalities.

DISCUSSION

In these experiments we could detect no differences in 4 strains of rats to the development of cardiac necrosis in response to isoproterenol, although the Sprague-Dawley animals were somewhat less sensitive in this respect. A direct relationship was seen between the severity of the lesions and the weight of the animals. Male rats were found to be more sensitive than females if a correlation is drawn according to age. If, however, male and female rats of similar weight are compared there is no difference in the severity of their cardiac lesions. Thus the greater sensitivity of the male animals can be attributed to their faster rate of growth. The greater susceptibility of old animals to the development of ischemic myocardial lesions has been mentioned. Hall, Ettinger, and Banting (8) found that young dogs were less sensitive than old to acetylcholine-induced myocardial necrosis. Dearing, Barnes, and Essex (5) were able to produce myocardial lesions with pitressin in old but not in young cats. It is not possible to consider the data in these studies in terms of weight as well as age of the animals. In recent studies in dogs (4) we have found that a similar relationship exists between body weight and sensitivity to isoproterenol myocardial toxicity.

The differences in sensitivity to isoproterenol related to the weight of the animal may explain the failure of Lands and associates (9) to observe myocardial toxicity in their experiments. These authors administered isoproterenol either orally or subcutaneously at 100 mg./kg. but most of the animals in their studies were small and for this reason would be unlikely to show severe lesions.

It was concluded in previous studies (2, 3, 12), that the cardiotoxicity of isoproterenol is related to its cardiovascular effects rather than

being a direct toxic effect exerted on the heart. Denison, Bardhanabaedya, and Green (6) have reported that isoproterenol causes dilatation of the coronary vessels; the basis of the myocardial necrosis therefore would not seem to be vascular occlusion or spasm. Isoproterenol is a strong cardiac stimulant agent (10) and also a peripheral depressor substance. The cardiac stimulation and the decrease of the available blood supply disturbs the balance between the oxygen need and blood supply of the myocardium and accounts for the hypoxemia and myocardial necrosis which is produced. This theory received further support in the results of the present experiment.

During growth of animals the size of the heart also increases; however, the heart weight/body weight relationship as shown decreases with the size of the rats. It is known that heart muscle does not develop hyperplasia; an increase in heart weight is due to increases in the length and bulk of individual muscle fibers. According to Wood (14) this growth of the myocardial fibers reduces availability of nutrition to the heart muscle. The nutritional needs of each muscle fiber depend on its cubic volume, whereas its blood supply is proportional to its surface area. Thus as the fiber grows in volume, there is the possibility of an increasing disparity between demand and supply, for the former is increasing by the cube, the latter by the square. The sensitivity of larger rats to the cardiotoxic effects of isoproterenol is probably related to a greater inability of these animals to maintain an adequate oxygen supply following myocardial stimulation.

SUMMARY

Isoproterenol produces myocardial necrosis irrespective of the strain of rats. There is a close correlation between the severity of the myocardial lesion and body weight. Age and sex seem to have an indirect influence, since body weight increases with age, and males of corresponding age are heavier than the females. The influence of weight on susceptibility to the cardiotoxic actions of isoproterenol further supports the hypoxemic origin of this experimental lesion.

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STUDY OF VITAMIN E SUPPLEMENTS IN RELATION TO MUSCULAR DYSTROPHY AND OTHER DISEASES IN AGING RATS*

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In a previous paper spontaneous muscular dystrophy and hindleg paralysis in aging rats were described (2). The lesions consisted of degeneration and necrosis affecting chiefly the gastrocnemius and adductor muscles and resembled the changes seen in experimental vitamin E deficiency. Although the vitamin E content of the diet was adequate according to accepted standards of maintenance level for the rat, it was possible that a relative deficiency could develop in old animals due to higher requirement. This hypothesis was tested by giving rats large supplements of alpha-tocopherol. In addition to studying the effect of alpha-tocopherol supplements on muscular dystrophy, observations were also made on other chronic diseases of aging rats, on body measurements, and on longevity.

MATERIALS AND METHODS

A total of 323 rats of both sexes and belonging to an inbred Sprague-Dawley strain were used. Details as to numbers examined at different ages are given in table 1. These animals were free from lung infection and were raised in air-conditioned quarters with uniform temperature, humidity, and regulated 12-hour periods of light and dark. They were weaned at 4 weeks of age and were kept on Rockland "D free" pellets fed ad libitum and replenished bi-weekly. According to bioassay the diet contained approximately 3.2 mg. alpha-tocopherol per 100 Gm. of pellets. The average daily intake of alpha-tocopherol was approximately 0.7 mg. for males consuming 20 Gm. of the diet and 0.42 mg. for females with a food intake of 13 Gm. These dietary levels of alpha-tocopherol were adequate for maintenance of adult males weighing 500 Gm. and of adult females weighing 300 Gm. (5). Growth and fertility on this diet had been excellent for the past 13 years. Rats fed only pellets were compared with rats given weekly supplements of 100 mg. alpha-tocopherol in 0.3 ml. of sesame oil* administered orally by use of a graduated medicine dropper. Rats receiving this additional alpha-tocopherol were divided into 2 groups: In Series I, supplements were started at weaning. In Series II, they were started at 364 days to 446 days of age. Separate controls were used for the 2 groups. Mothers of animals in Series I also received extra alpha-tocopherol during gestation.

Body weights were terminal values. Tibia length was determined by precision calipers and was the distance between the spines of the tibial head and the medial malleolus. Body length was the calipered measurement from the tip of the nose to the anus.

Most of the rats were killed by intraperitoneal injection of nembutal when they were moribund or had hindleg paralysis. A few died spontaneously and were examined before autolysis set in. Complete autopsies were performed immediately after animals were killed. Specimens were taken from all tissues and, after fixation in Zenker's fluid, they were imbedded in paraffin. Sections were stained with hematoxylin and eosin. The following skeletal muscles were selected for histologic study: the gastrocnemius and adductors of the hindlegs, the flexors of the forelegs, the diaphragm, and the abdominal and pectoral muscles.

RESULTS

Muscular Degeneration—As described in an earlier paper (2), hindleg paralysis or weakness corresponded roughly to severity of muscle degeneration affecting chiefly the gastronemius and adductors of the hindlegs. Muscle fibers were involved singly or in groups. Loss of cross striations was the earliest histologic evidence of degeneration. Later there was fragmentation and disintegration of fibers and sometimes infiltration by fat. Finally, only collapsed sarcolemma sheaths remained.

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* Generously supplied by Hoffmann-La Roche, Nutley, N. J., through the courtesy of Dr. L. A. Pirk.

Incidence of Muscle Lesions—Tables 1, 2, and 3 give the comparative incidence of histologically observed muscle lesions in rats with and without dietary supplements of alpha-tocopherol. Except for three instances of slight lesions in the untreated animals not included in the tables, all observed muscle changes were of moderate or marked severity. In spite of supplements, frequency of lesions increased with advancing age in much the same manner as previously reported (2, 6).

In table 1 complete data on frequency of lesions in rats at all ages in both series are shown. Onset of lesions was later in females than in males (2). Due to the small number of rats in some age groups, percentage incidence is not given in this table.

Since muscle lesions were rare in males under 700 days old and in females less than 800 days old, total incidence in rats over these ages was used to compare the findings in animals of Series I and II with and without alpha-tocopherol supplements (table 2). Frequency of lesions in both sexes was higher in Series II than in Series I, but differences in each Series between treated and untreated animals were not statistically significant. Greater susceptibility of rats in Series II to muscular dystrophy could be due to accidental selection or genetic differences.

TABLE 1. MUSCULAR DYSTROPHY IN RATS WITH AND WITHOUT ALPHA-TOCOPHEROL SUPPLEMENTS. INCIDENCE OF MODERATE OR MARKED MUSCLE LESIONS AT DIFFERENT AGES OBSERVED HISTOLOGICALLY.

Age Range at Autopsy (Days)	Without Alpha-Tocopherol Supplement			With Alpha-Tocopherol Supplement		
	Mean Age (Days)	No. of Rats	No. with Lesions	Mean Age (Days)	No. of Rats	No. with Lesions
Males, Series I. Supplements started at weaning (28 days of age).						
300 - 699	610	20	1	597	30	0
700 - 799	755	15	0	746	14	1
800 - 899	843	10	5	830	5	1
900 - 999	910	2	2	931	1	0
Totals:		47	8		50	2
Males, Series II. Supplements started at 364 to 446 days of age.						
600 - 699	677	7	0	683	5	0
700 - 799	745	18	5	750	14	5
800 - 899	847	8	7	849	11	5
900 - 999	937	5	5	935	8	4
Totals:		38	17		38	14
Females, Series I. Supplements started at weaning (28 days of age).						
400 - 799	630	13	0	670	22	0
800 - 899	845	14	0	835	13	2
900 - 999	951	17	10	940	10	0
1000 - 1199	1076	7	6	1093	7	7
Totals:		51	16		52	9
Females, Series II. Supplements started at 369 to 444 days of age.						
606	606	1	0			
700 - 799	749	3	0			
800 - 899	862	7	2	851	5	0
900 - 999	940	7	5	962	9	8
1000 - 1299	1061	10	9	1160	5	5
Totals:		28	16		19	13

TABLE 2. MUSCULAR DYSTROPHY IN MALE RATS OVER 700 DAYS OLD AND IN FEMALES OVER 800 DAYS OLD WITH AND WITHOUT ALPHA-TOCOPHEROL SUPPLEMENTS.

INCIDENCE OF MODERATE OR MARKED LESIONS OBSERVED HISTOLOGICALLY IN SERIES I AND SERIES II.

Age Range (Days)	Without Alpha-Tocopherol Supplement			With Alpha-Tocopherol Supplement		
	No. of Rats	No. with Lesions	% with Lesions	No. of Rats	No. with Lesions	% with Lesions
Males, Series I						
700 - 999	27	7	26	20	2	10
Males, Series II						
700 - 999	31	17	55	33	14	42
Females, Series I						
800 - 1199	38	16	42	30	9	30
Females, Series II						
800 - 1299	24	16	67	19	13	68

TABLE 3. MUSCULAR DYSTROPHY IN MALE RATS OVER 700 DAYS OLD AND IN FEMALES OVER 800 DAYS OLD WITH AND WITHOUT ALPHA-TOCOPHEROL SUPPLEMENTS.

COMBINED INCIDENCE (SERIES I AND II) OF MODERATE OR MARKED MUSCLE LESIONS OBSERVED HISTOLOGICALLY.

Age Range (Days)	Without Alpha-Tocopherol Supplement			With Alpha-Tocopherol Supplement		
	No. of Rats	No. with Lesions	% with Lesions	No. of Rats	No. with Lesions	% with Lesions
Males						
700 - 799	33	5	15	28	6	21
800 - 899	18	12	67	16	6	38
900 - 999	7	7	100	9	4	44
Total over 700 days	58	24	41	53	16	30
Females						
800 - 899	21	2	10	18	2	11
900 - 999	24	15	63	19	8	42
1000 - 1299	17	15	88	12	12	100
Total over 800 days	62	32	52	49	22	45

TABLE 4. MEASUREMENTS OF RATS WITH AND WITHOUT ALPHA-TOCOPHEROL SUPPLEMENTS.

	Without Alpha-Tocopherol Supplement				With Alpha-Tocopherol Supplement			
	No.	Mean	S.D	Range	No.	Mean	S.D.	Range
Males, Series I								
600-699 days of age								
Tibia Length (cm.)	12	4.61	0.07		18	4.60	0.13	
Body Length (cm.)	12	23.8	0.8		17	24.0	0.9	
Body Weight (Gm.)	12	384		264-562	17	365		218-526
700-799 days of age								
Tibia Length (cm.)	21	4.66	0.11		14	4.59	0.07	
Body Length (cm.)	17	24.3	0.9		12	24.1	0.5	
Body Weight (Gm.)	20	357		247-516	13	372		238-469
800-899 days of age								
Tibia Length (cm.)	10	4.66	0.07		5	4.50	0.03	
Body Length (cm.)	10	24.2	0.8		5	23.3	0.2	
Body Weight (Gm.)	9	360		284-505	5	319		282-380
Males, Series II								
600-699 days of age								
Tibia Length (cm.)	8	4.67	0.04		5	4.60	0.06	
Body Length (cm.)	8	24.2	1.2		5	24.3	0.5	
Body Weight (Gm.)	8	354		246-416	5	333		300-372
700-799 days of age								
Tibia Length (cm.)	19	4.60	0.09		12	4.60	0.09	
Body Length (cm.)	16	24.4	0.7		12	24.2	0.5	
Body Weight (Gm.)	19	336		216-485	12	354		252-458
800-899 days of age								
Tibia Length (cm.)	8	4.60	0.09		10	4.65	0.07	
Body Length (cm.)	8	23.8	0.9		9	24.4	1.0	
Body Weight (Gm.)	8	328		244-443	10	380		307-447
900-999 days of age								
Tibia Length (cm.)	5	4.61	0.07		8	4.61	0.11	
Body Length (cm.)	4	24.3	0.2		9	24.5	1.0	
Body Weight (Gm.)	4	333		314-358	9	367		310-440
Females, Series I								
800-899 days of age								
Tibia Length (cm.)	14	4.02	0.08		14	4.02	0.09	
Body Length (cm.)	12	20.6	0.8		12	21.1	0.4	
Body Weight (Gm.)	14	219		140-292	13	219		188-285
900-999 days of age								
Tibia Length (cm.)	17	4.02	0.10		10	4.00	0.06	
Body Length (cm.)	17	20.8	0.6		9	21.0	0.6	
Body Weight (Gm.)	17	217		170-284	9	220		180-265
1000-1199 days of age								
Tibia Length (cm.)	7	4.04	0.09		7	3.97	0.13	
Body Length (cm.)	7	20.8	0.5		7	20.4	1.1	
Body Weight (Gm.)	7	208		192-241	7	228		185-268
Females, Series II								
800-899 days of age								
Tibia Length (cm.)	7	4.01	0.04		5	4.00	0.05	
Body Length (cm.)	5	21.0	0.2		5	21.4	0.9	
Body Weight (Gm.)	6	233		198-285	5	234		206-258
900-999 days of age								
Tibia Length (cm.)	8	4.00	0.05		9	4.07	0.04	
Body Length (cm.)	8	20.8	0.5		6	21.3	0.6	
Body Weight (Gm.)	8	236		182-320	9	229		185-276
1000-1299 days of age								
Tibia Length (cm.)	9	4.00	0.05		5	4.00	0.08	
Body Length (cm.)	8	20.9	0.8		5	21.0	0.5	
Body Weight (Gm.)	9	247		178-366	5	211		195-236

In table 3 the data of Series I and II are combined and incidence of lesions in the three oldest age groups of males and females with and without supplements of alpha-tocopherol is given. Frequency of lesions in both sexes increased with advancing age. Although there was a lower incidence of muscular degeneration in the treated rats than in the untreated ones, the differences were not statistically significant.

Incidence of Atrophic Testes—Since the testes may be affected by vitamin E deficiency, changes as determined by microscopic examination were recorded. Combined incidence of atrophy in both series was 39% in rats without added alpha-tocopherol in the diet and 28% in rats with dietary supplements of alpha-tocopherol. In the remaining animals, the testes and epididymides contained large numbers of spermatozoa.

Measurements.—Table 4 shows measurements of male and female rats of both Series in the older age groups. In a previous study it was found that increments in skeletal growth were extremely small after 1 year in males and after 6 months in females (4). Data in table 4 show that there were no significant differences in tibia length or body length of males over 600 days old and of females over 800 days old with or without supplements of alpha-tocopherol. Skeletal measurements were not affected by the chronic diseases that developed in these animals. but body weight was sharply reduced (4). All measurements were higher in males than in females.

Other Chronic Diseases.—Principal findings at autopsy exclusive of muscular dystrophy and tumors were chronic glomerulonephritis, periarteritis, and myocardial degeneration. These diseases appeared earlier than muscular dystrophy and onset was sooner in males than in females (2).

Initial changes in chronic glomerulonephritis consisted of dilatation of the lumina of convoluted tubules by casts. With further obstruction the collecting tubules also became dilated and the connecting glomeruli underwent atrophy, hyalinization, and fibrosis. Fi-

TABLE 5. INCIDENCE OF CARDIAC, VASCULAR, AND RENAL LESIONS IN RATS WITH AND WITHOUT ALPHA-TOCOPHEROL SUPPLEMENTS.

	Without Alpha-Tocopherol Supplement			With Alpha-Tocopherol Supplement		
	No. of Rats and Age Range	No. with Lesions	% with Lesions	No. of Rats and Age Range	No. with Lesions	% with Lesions
Males, Series I	43 (476-914 days)			48 (317-931 days)		
Glomerulonephritis		43	100		47	98
Periarteritis		28	65		37	77
Myocardial Degeneratian		38	90		35	73
Males, Series II	38 (657-979 days)			38 (676-975 days)		
Glomerulonephritis		38	100		36	95
Periarteritis		27	71		23	61
Myocardial Degeneration		27	71		27	71
Females, Series I	51 (415-1147 days)			52 (417-1155 days)		
Glomerulonephritis		36	71		48	92
Periarteritis		10	20		19	37
Myocardial Degeneration		27	53		22	42
Females, Series II	28 (606-1228 days)			19 (805-1215 days)		
Glomerulonephritis		15	54		16	84
Periarteritis		2	7		3	16
Myocardial Degeneration		12	43		12	63

TABLE 6. SURVIVAL OF RATS WITH AND WITHOUT ALPHA-TOCOPHEROL SUPPLEMENTS STARTED AT WEANING (SERIES I).

Age Range (Days)	Males				Females			
	Without Alpha-Tocopherol (47)		With Alpha-Tocopherol (50)		Without Alpha-Tocopherol (51)		With Alpha-Tocopherol (52)	
	Mean Age (Days)	% Alive	Mean Age (Days)	% Alive	Mean Age (Days)	% Alive	Mean Age (Days)	% Alive
300 - 699	610	57	597	40	630	75	670	58
700 - 799	755	26	746	12				
800 - 899	843	4	830	2	845	47	835	33
900 - 999	910	0	931	0	951	14	940	13
1000 - 1199					1076	0	1093	0

nally, the cortex was honeycombed with small cysts representing greatly dilated tubules. There was a relative increase of interstitial connective tissue and the media of the small renal arteries was thickened. Hypertension and cardiac hypertrophy (1, 3), hydrothorax and uremia were late complications.

Periarteritis involved first the pancreatic and spermatic vessels and then the mesenteric vessels. Other arteries were also affected but to a much lesser degree. The main renal arteries were never involved, but small cortical branches occasionally showed changes. Grossly, the vessels had a beaded appearance and microscopically there were focal degenerative and inflammatory changes in the media and intima. Aneurysms were common and sometimes ruptured. Ascites was a frequent finding but intestinal infarction was rare.

Myocardial changes consisted of degeneration and fibrosis and occurred chiefly in the papillary muscle and adjacent myocardium of the left ventricle, in the base and at the apex of the heart.

Frequency of cardiac, renal, and vascular disease in rats with and without supplements of alpha-tocopherol is shown in table 5. There were no significant differences in percentage incidence of lesions in untreated and treated males and females of both series.

Tumors—In order of frequency, the most common benign tumors were fibroadenomas of the female breast, pheochromocytomas of the adrenal, chromophobe adenomas of the pituitary, adenomas of the thyroid, and islet cell adenomas of the pancreas. These tumors occurred about equally in all groups.

The number of malignant tumors was too small to be suitable for comparative study. Fibrosarcomas were present in all groups and in both sexes. Malignant myxomas and epidermoid carcinomas were found only in females. Of particular interest was the occurrence of 4 breast carcinomas and 2 lymphomas in females and 2 lymphomas in males, all in rats receiving alpha-tocopherol supplements. These tumors are extremely rare in our rat strain.

Survival rates—Survival rates of only Series I rats are recorded in table 6 because data for Series II did not cover the entire life span. Chief causes of death, or of moribund condition, were chronic glomerulonephritis, periarteritis, muscular dystrophy, and tumors. Due to earlier onset of renal and vascular diseases, the percentage of male and female survivors at different ages was lower in rats receiving alpha-tocopherol supplements than in those without supplements. In both groups, females outlived males due to later onset of diseases in females (2, 4).

DISCUSSION

If the muscular dystrophy in aging rats were due to vitamin E deficiency, then the principal diseases that might contribute to this condition would be chronic glomerulonephritis and periarteritis. These diseases setting in before the onset of muscular dystrophy could cause a vitamin depletion and/or intestinal malabsorption against which even large supplements of alpha-tocopherol would be ineffective. However, there was no relation between incidence or severity of renal or vascular disease and muscle lesions. For example, in 750-day-old males without alpha-tocopherol supplements, all had glomerulonephritis, 70% had periarteritis, yet none developed muscular dys-

trophy. In rats of the same age receiving supplements, incidence of renal and vascular diseases was 100% and 90%, respectively, while muscle lesions occurred in 8%.

SUMMARY

Large supplements of alpha-tocopherol failed to prevent the muscular dystrophy of aging rats. Other chronic diseases, longevity, and growth were also unaffected.

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THE ADENYLPYROPHOSPHATASE, INORGANIC PYROPHOSPHATASE, AND PHOSPHOMONOESTERASE ACTIVITIES OF HUMAN ARTERIAL TISSUE IN INDIVIDUALS OF VARIOUS AGES*

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The presence in human arterial tissue of a high adenylpyrophosphatase activity was first reported by Baló, Banga, and Josepovits (3) in 1948; the study was subsequently extended by Banga and Nowotny (4, 5). According to these investigators the hydrolysis of adenosinetriphosphate by the arterial tissue is catalyzed by two different enzymes, one of which is bound to myosin and has a pH optimum at 7, whereas the other is water-soluble and exhibits a maximum activity at pH 9. The latter enzyme, which has been found only in arterial tissue, was designated aorta-adenylpyrophosphatase; one of the characteristics of the enzyme is its ability to split off orthophosphate from both adenosinetriphosphate and adenosinediphosphate.

Following the initial publications by these authors fairly extensive studies have been made on the activities of enzymes in arterial tissue capable of causing dephosphorylation of adenosinetriphosphate. The investigations include observations on vascular tissue samples from several animal species (2, 4, 6, 8, 12) and on a limited number of human arterial samples (2, 4, 5). The reported results indicate that considerable differences exist between the enzyme activities in various animals and between various types of arteries in the same animals. The presence in the coronary artery tissue of cattle of a notable myokinase activity has further been reported by Carr and his associates (7, 9); this enzyme catalyzes the conversion of adenosinediphosphate to adenosinetriphosphate and adenosinemonophosphate, a reaction which likewise results in the formation of adenosinemonophosphate as the end product. The presence of 5-nucleotidase in human aortic tissue was demonstrated by Reis (1, 14). A phosphomonoesterase activity of human aortic tissue with a pH optimum at 5.6-5.7 was reported by this author in 1950 (10).

The present investigation was undertaken with the purpose of determining the rate of dephosphorylation of adenosinetriphosphate by human arterial tissue samples obtained at autopsy from subjects of various ages. Because the individual enzymes responsible for the dephosphorylation of adenosinetriphosphate have not been isolated in pure form from arterial tissue the total dephosphorylating activity, as measured under the conditions employed in the present study, will be designated as adenylpyrophosphatase activity. In addition to the adenylpyrophosphatase activity determinations were made of the inorganic pyrophosphatase and phosphomonoesterase activities of the samples.

MATERIALS AND METHODS

Eighty-six samples of the aorta, 81 samples of the pulmonary artery, and 50 samples of the coronary artery were included in the study.† The enzyme activity determinations were performed on freshly prepared aqueous homogenates. In the case of the aortic and coronary artery samples measurements were made both on normal and arteriosclerotic tissue sections of the same blood vessels. All reagents used in the experiments were prepared with glass-distilled water. The tissue nitrogen analyses were carried out by macro-Kjeldahl procedure or by the gasometric technique of Van Slyke and Kugel (15). For the cholesterol determinations the procedure of Knobil and associates was used (11). The tissue content of inorganic phosphate was recorded as a measure of the degree of calcification present in the samples.

Adenylpyrophosphatase—The final millimolar concentrations used (total volume, 4.75 ml.) were : adenosinetriphosphate disodium, 1.5; magnesium chloride, 1.0; tris(hydroxymethyl)aminomethane, 16.0; 2-amino-2-methyl-1,3-propanediol, 16.0; HCl, 16.0; the pH of the buffer-substrate mixture was 8.1. An amount of homogenate corresponding to 10 to 50 mg. of fresh tissue was employed in each test.

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A tissue test without addition of adenosinetriphosphate was run with each sample and reagent blanks with and without adenosinetriphosphate with each set of analyses. Glassware cleaned with warm HCl and rinsed with glass-distilled water was used throughout the tests.

The samples were incubated for 30 min. at 38 C. and 1.0 ml. aliquots of the incubation mixture were removed at 0 and 30 min. Each aliquot was added to 0.2 ml. of 30% trichloroacetic acid contained in a test tube placed in ice water. After centrifugation, 500 cu.mm. of the supernatants were used for determination of orthophosphate. The colorimetric phosphate determinations were performed by addition of 5.0 ml. of freshly prepared acetate-molybdate-ascorbic acid reagent of the composition described by Lowry, Roberts, Wu, Hixon, and Crawford (13). The readings were made in a Beckman DU spectrophotometer at 650 millimicrons. The molar extinction coefficient observed for phosphate under these conditions was 3600; the results of the analyses were found to be closely reproducible.

The K_m observed for adenosinetriphosphate was 5.1×10^{-4} M. Studies on the effect of the magnesium concentration on the enzyme activity revealed the highest activity at a concentration of 1.0 mM; the activities observed at 0.5, 2.0, 2.5, and 5.0 mM concentrations were, respectively, 71, 89, 81, and 71% of the activity recorded at the 1.0 mM concentration.

An investigation was made of the correlation between enzyme activity and time of incubation. The results revealed linearity between the incubation period and the amounts of inorganic phosphate liberated until a quantity of phosphate approximately equalling that of one phosphate group of the adenosinetriphosphate substrate had been released; after this stage had been reached the activity curve resembled that of a first order reaction. A close correlation was noted within the first stage of the test between the quantities of tissue used and the amounts of phosphate liberated.

Inorganic Pyrophosphatase—The final millimolar concentrations used (total volume, 5.0 ml.) were: sodium pyrophosphate, 1.0; magnesium chloride, 15.0; barbital, 60.0 ; the pH of the buffer-substrate mixture was 7.2. The sodium pyrophosphate solution was added to the buffer before the magnesium chloride solution to prevent precipitation of magnesium pyrophosphate. An amount of homogenate corresponding to 10 to 25 mg. of fresh tissue was employed in each test; the incubation period used (38 C.) was 30 min. The performance of reagent blanks, tissue blanks, protein precipitation, and colorimetric phosphate determination was carried out in a manner similar to that described for the adenylpyrophosphatase procedure.

The K_m observed for sodium pyrophosphate under the conditions of the method was 4.2×10^{-4} M. Experiments were conducted to investigate the relation between the magnesium chloride concentration and the pyrophosphatase activity; in these tests, as in the finally developed procedure described above, the pyrophosphate solution was added to the buffer before the magnesium chloride reagent. The results, presented in figure 1, show a maximum enzyme activity at a 15.0 millimolar magnesium chloride concentration in the presence of 1.0 millimolar sodium pyrophosphate.

After the establishment of an optimal molar magnesium chloride/sodium pyrophosphate ratio of 15, further experiments were carried out in which this ratio was maintained and the pyrophosphate concentration varied from 0.2 to 4.0 mM. The activity was found to increase with the pyrophosphate concentration from 0.2 to 1.0 mM, the recorded values for 0.2, 0.4, and 0.6 millimolar concentrations being, respectively, 45, 78, and 86% of the activity measured at the 1.0 millimolar concentration. Since an increase in the sodium pyrophosphate concentration to 2.0 mM resulted in a visible precipitation of magnesium pyrophosphate after 15 min., and an increase to 4.0 mM was followed by an instantaneous precipitation, the 1.0 mM sodium pyrophosphate concentration was chosen for the activity measurements. It should be noted that this concentration is 2.4 times the observed K_m value. A satisfactory proportionality was noted between the quantities of tissue used and recorded enzyme activities over a 30-min. incubation period.

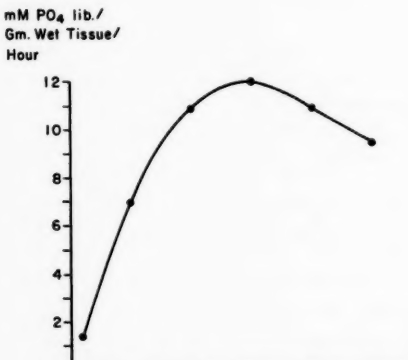

Fig. 1. Effect of magnesium chloride concentration on the inorganic pyrophosphatase activity of aortic tissue homogenate.

Phosphomonoesterase—The final millimolar concentrations used (total volume, 6.0 ml.) were : paranitrophenylphosphate, 6.25; magnesium chloride, 4.0 : citric acid-sodium citrate, 120.0; the pH of the buffer-substrate mixture was 5.6. An amount of homogenate corresponding to 25 mg. of fresh tissue was employed in each test. A reagent blank was run with each set of analyses.

The samples were incubated for 30 min. at 38 C., and 2.0 ml. aliquots of the incubation mixture were removed at 0 and 30 min. Each aliquot was added to 1.0 ml. of 30% trichloroacetic acid contained in a test tube placed in ice water. After centrifugation, 1.0 ml. of the supernatant was pipetted into a test tube, and 3.0 ml. of 1 N NaOH were added. The color development was performed in duplicate, and the colorimetric readings were made at 410 millimicrons, using a Beckman DU spectrophotometer.

The molar extinction coefficient observed for paranitrophenol was 17,500, a value which is similar to that reported by Lowry, Roberts, Wu, Hixon, and Crawford (13). The K_m found for paranitrophenylphosphate was 1.5×10^{-3} M. A high degree of proportionality was noted between time of incubation and recorded enzyme activities over a 40-minute period, and between the quantities of tissue employed and the measured activities over a 10 to 50 mg. range.

RESULTS

A. Investigations on Degree of Specificity of Measured Phosphatase Activities

The problem of the identity of the enzymes responsible for the adenylpyrophosphatase and inorganic pyrophosphatase activities observed in various tissues has been the subject of rather extensive investigation and discussion. In connection with the present study experiments were carried out with the purpose of elucidating this point with regard to human arterial tissue. In addition, the degree of interference of 5-nucleotidase with the dephosphorylation of adenosinetriphosphate and of the unspecific phosphomonoesterase with the dephosphorylation of adenosinetriphosphate and inorganic pyrophosphate was studied. All the comparative measurements were carried out on the same homogenates.

The results of the experiments designed for the study of the identity or non-identity of the adenylpyrophosphatase and inorganic pyrophosphatase activities are presented in figure 2. In one of the experimental series (curves A and B) the standard substrate and magnesium concentrations were employed as listed under "Methods." For investigation of the effect of pH on the activities the buffer used for the particular enzyme was adjusted to pH 6.9, 7.2, 7.5, 7.8, 8.1, and 8.4. As seen from the figure the observed pH optimum for the adenylpyrophosphatase activity was found to be 8.1, and for the inorganic pyrophosphatase activity 7.1-7.2. In order to exclude effects of the types of buffer employed, additional studies were carried out in which the buffers were interchanged (curves C and D). As recorded in the figure the interchange of the buffers had little effect on the enzyme activities or on the pH optima. An additional series of experiments was then undertaken in which the adenylpyrophosphatase activity was measured at the magnesium chloride concentration employed in the inorganic pyrophosphatase experiments (15.0 millimolar concentration, curve E) and

the inorganic pyrophosphatase activity recorded at the magnesium chloride concentration used in the adenylpyrophosphatase studies (1.0 millimolar concentration, curve F). It will be seen from the figure (curve E) that the increase of the magnesium concentration to a 15.0 millimolar level caused a definite, although moderate, inhibition of the adenylpyrophosphatase activity, as would have been expected from the previously conducted experiments on the magnesium dependency of that enzyme. It should further be noted that only a minimal phosphatase activity was observed when inorganic pyrophosphate was used as substrate in the presence of a 1.0 millimolar magnesium chloride concentration (curve F).

The demonstration of different pH optima and of different magnesium requirements for the two types of enzyme activities suggests that arterial adenylpyrophosphatase and inorganic pyrophosphatase are not identical enzymes. The requirement of a high magnesium concentration for the activation of the inorganic pyrophosphatase probably explains the failure of Baló, Banga, and Josepovits (3) to detect the presence of this enzyme in human arterial tissue.

In the evaluation of the recorded activities of adenylpyrophosphatase and inorganic pyrophosphatase various

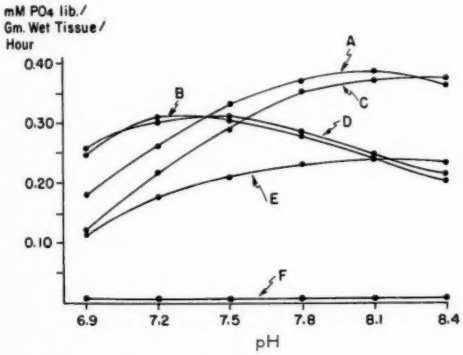

Fig. 2. Adenylpyrophosphatase and inorganic pyrophosphatase activities of the same aortic homogenate, as measured under different conditions.

Curve A: Adenylpyrophosphatase activity using tris and 2-amino-2-methyl-1,3-propanediol buffer and 1.0 millimolar magnesium chloride concentration.

Curve B: Inorganic pyrophosphatase activity using barbital buffer and 15.0 millimolar magnesium chloride concentration.

Curve C.: Adenylpyrophosphatase activity using barbital buffer and 1.0 millimolar magnesium chloride concentration.

Curve D: Inorganic pyrophosphatase activity using tris and 2-amino-2-methyl-1,3-propanediol buffer and 15.0 millimolar magnesium chloride concentration.

Curve E.: Adenylpyrophosphatase activity using tris and 2-amino-2-methyl-1,3-propanediol buffer and 15.0 millimolar magnesium chloride concentration.

Curve F.: Inorganic pyrophosphatase activity using barbital buffer and 1.0 millimolar magnesium chloride concentration.

other aspects must be considered. With regard to adenylpyrophosphatase the ability of this enzyme to remove not only the terminal phosphate group from adenosinetriphosphate, but also a phosphate group from adenosinediphosphate has been pointed out by Banga and Nowotny (4). This fact was confirmed in the present study through the kinetic investigations previously mentioned and through the finding of a notable liberation of orthophosphate from adenosinediphosphate under the conditions employed for the adenylpyrophosphatase measurements. As the result of the action of this enzyme on adenosinediphosphate a certain amount of adenosinemonophosphate will be released which may serve as a substrate for 5-nucleotidase. In order to establish the extent to which 5-nucleotidase might interfere with the adenylpyrophosphatase determinations parallel experiments were carried out with the same homogenates in which, respectively, adenosinetriphosphate and adenosinemonophosphate were employed as substrates, the conditions otherwise being similar to those used in the adenylpyrophosphatase tests. The observed 5-nucleotidase activity was found to be of the same order of magnitude as that of adenylpyrophosphatase, which suggests that 5-nucleotidase may contribute notably to the liberation of inorganic phosphate in the adenylpyrophosphatase tests if these are continued to a stage where appreciable quantities of adenylmonophosphate are made available for the enzyme.

Although the unspecific phosphomonoesterase is capable of hydrolyzing both adenosinetriphosphate and inorganic pyrophosphate the interference by this enzyme in the activity measurements of adenylpyrophosphatase and inorganic pyrophosphatase was found to be fairly small under the experimental conditions employed in the present study. This is explainable by the facts 1) that the arterial phosphomonoesterase possesses an optimal activity at pH 5.6-5.7 (10) and exhibits only moderate activity at pH 7.2 and 8.1, and 2) that the phosphomonoesterase activity of human arterial tissue, even when measured under optimal conditions, is considerably lower than the activities of adenylpyrophosphatase and inorganic pyrophosphatase. For verification of these points a series of experiments was conducted in which paranitrophenylphosphate was added to the substrate-buffer mixtures used in the adenylpyrophosphatase and inorganic pyrophosphatase tests, and the quantities of paranitrophenol liberated by the homogenates were determined. The average phosphomonoesterase activities measured under these conditions at pH 7.2 and 8.1 were found to be, respectively, 27.7% (range 26.9-28.2) and 6.6% (range 4.2-8.3) of the activities observed in simultaneously performed regular phosphomonoesterase determinations at pH 5.6. The calculated phosphate liberation by the phosphomonoesterase at pH 7.2 was 9.4% (range 8.5-10.4) of the activity exhibited by the inorganic pyrophosphatase, and at pH 8.2 was 1.4% (range 1.1-1.8) of the activity of the adenylpyrophosphatase of the same homogenates.

B. Phosphatase Activities of Arterial Samples

The mean enzyme activities of aortic, pulmonary artery, and coronary artery samples observed for various age groups have been listed in table 1.

TABLE 1. MEAN PHOSPHATASE ACTIVITIES OF HUMAN ARTERIAL TISSUE IN VARIOUS AGE GROUPS.

Age Group (Years)	N	Cholesterol, % of Wet Weight	Adenylpyrophosphatase				Inorganic Pyrophosphatase				Phosphomonoesterase			
			mM PO_4 lib./Gm. Wet Tissue/Hour	s.d. of distr.	mM PO_4 lib./Gm. Tissue N/Hour	s.d. of distr.	mM PO_4 lib./Gm. Wet Tissue/Hour	s.d. of distr.	mM PO_4 lib./Gm. Tissue N/Hour	s.d. of distr.	mM PO_4 lib./Gm. Wet Tissue/Hour	s.d. of distr.	mM PO_4 lib./Gm. Tissue N/Hour	s.d. of distr.
Normal Aortic Tissue														
0 - 9	17	0.2	0.22	0.08	5.3	2.6	0.15	0.08	3.7	2.1	0.024	0.009	0.6	0.2
10 - 19	5	0.3	0.26	0.03	7.3	1.8	0.29	0.06	8.7	4.2	0.044	0.012	1.2	0.4
20 - 29	2	0.5	0.28	—	7.4	—	0.24	—	6.2	—	0.054	—	1.4	—
30 - 39	7	0.4	0.20	0.05	5.1	1.2	0.16	0.04	3.8	0.8	0.046	0.008	1.2	0.3
40 - 49	12	0.6	0.21	0.07	5.7	1.7	0.19	0.04	5.2	0.9	0.049	0.009	1.3	0.3
50 - 59	21	0.6	0.20	0.05	5.6	1.7	0.14	0.04	3.9	1.5	0.042	0.009	1.2	0.3
60 - 69	19	0.7	0.19	0.06	5.2	1.8	0.14	0.06	4.0	1.6	0.048	0.017	1.3	0.5
70 - 85	4	0.7	0.20	—	6.1	—	0.19	—	6.0	—	0.036	—	1.2	—
Grand Mean			0.21	0.07	5.6	2.0	0.16	0.03	4.5	2.2	0.041	0.014	1.1	0.4
Arteriosclerotic Aortic Tissue														
10 - 19	1	0.8	0.30	—	6.9	—	0.29	—	6.5	—	0.053	—	1.2	—
20 - 29	1	0.6	0.30	—	8.7	—	0.24	—	6.9	—	0.053	—	1.5	—
30 - 39	4	0.5	0.17	—	4.1	—	0.13	—	3.2	—	0.036	—	0.9	—
40 - 49	12	1.3	0.20	0.11	5.6	3.1	0.17	0.04	4.8	1.5	0.043	0.009	1.2	0.3
50 - 59	20	1.7	0.16	0.06	4.7	1.9	0.12	0.05	3.6	1.7	0.043	0.014	1.3	0.4
60 - 69	18	1.3	0.16	0.05	4.3	1.7	0.13	0.06	3.5	1.9	0.042	0.012	1.2	0.4
70 - 85	4	2.5	0.10	—	3.4	—	0.11	—	3.9	—	0.038	—	1.4	—
Grand Mean			0.17	0.08	4.9	2.2	0.17	0.07	3.9	1.8	0.042	0.012	1.3	0.4
Pulmonary Artery Tissue														
0 - 9	13	0.2	0.23	0.10	6.0	3.1	0.13	0.06	3.3	1.5	0.019	0.007	0.5	0.2
10 - 19	5	0.3	0.24	0.12	6.4	3.4	0.39	0.09	9.9	0.3	0.028	0.011	0.7	0.3
20 - 29	2	0.2	0.36	—	9.7	—	0.30	—	7.9	—	0.039	—	1.1	—
30 - 39	7	0.2	0.26	0.06	6.9	2.3	0.18	0.06	4.8	1.7	0.030	0.008	0.8	0.1
40 - 49	12	0.3	0.28	0.09	8.1	2.5	0.26	0.08	7.4	2.2	0.038	0.007	1.1	0.3
50 - 59	21	0.4	0.26	0.05	7.9	2.2	0.19	0.07	5.7	2.4	0.034	0.007	1.1	0.3
60 - 69	17	0.4	0.23	0.05	6.8	1.7	0.18	0.08	5.4	1.8	0.038	0.012	1.1	0.4
70 - 85	4	0.4	0.18	—	5.6	—	0.17	—	5.2	—	0.025	—	0.8	—
Grand Mean			0.25	0.08	7.1	2.4	0.20	0.09	5.7	2.5	0.032	0.011	0.9	0.4
Normal Coronary Artery Tissue														
0 - 9	4	0.2	0.32	—	6.7	—	0.27	—	4.9	—	0.026	—	0.4	—
10 - 19	4	0.3	0.18	—	4.1	—	0.41	—	9.1	—	0.030	—	1.1	—
20 - 29	2	0.1	0.44	—	14.0	—	0.44	—	13.6	—	0.040	—	1.3	—
30 - 39	6	0.2	0.44	0.15	13.5	6.1	0.33	0.12	10.1	4.2	0.027	0.013	0.8	0.4
40 - 49	9	0.5	0.34	0.17	8.8	6.4	0.36	0.10	10.5	3.5	0.035	0.006	0.9	0.2
50 - 59	10	0.4	0.53	0.15	13.5	4.5	0.30	0.10	8.3	3.6	0.032	0.009	0.8	0.3
60 - 69	11	0.5	0.53	0.20	15.7	8.2	0.43	0.26	13.8	6.4	0.034	0.012	1.2	0.6
70 - 85	4	0.5	0.37	—	13.7	—	0.21	—	7.8	—	0.033	—	1.3	—
Grand Mean			0.43	0.19	12.5	6.5	0.34	0.14	10.1	4.5	0.032	0.011	1.0	0.5

TABLE 1. MEAN PHOSPHATE ACTIVITIES OF HUMAN ARTERIAL TISSUE IN VARIOUS AGE GROUPS. (CONTINUED.)

Age Group (Years)	N	Cholesterol, % of Wet Weight	Adenylpyrophosphatase				Inorganic Pyrophosphatase				Phosphomonoesterase			
			mM PO_4 lib./Gm. Wet Tissue/Hour	s.d. of distr.	mM PO_4 lib./Gm. Tissue N/Hour	s.d. of distr.	mM PO_4 lib./Gm. Wet Tissue/Hour	s.d. of distr.	mM PO_4 lib./Gm. Tissue N/Hour	s.d. of distr.	mM PO_4 lib./Gm. Wet Tissue/Hour	s.d. of distr.	mM PO_4 lib./Gm. Tissue N/Hour	s.d. of distr.
Arteriosclerotic Coronary Artery Tissue														
20 - 29	1	0.4	0.44	—	15.1	—	0.30	—	10.3	—	0.035	—	1.2	—
30 - 39	1	0.2	0.30	—	9.4	—	0.42	—	13.2	—	0.028	—	0.9	—
40 - 49	7	2.5	0.34	0.16	11.2	4.9	0.24	0.11	7.7	3.4	0.048	0.022	1.5	0.9
50 - 59	18	2.3	0.31	0.15	11.0	5.9	0.22	0.09	7.8	4.3	0.042	0.019	1.6	0.8
60 - 69	15	2.0	0.34	0.19	11.1	6.8	0.27	0.16	8.1	3.7	0.040	0.011	1.4	0.5
70 - 85	4	2.4	0.33	—	8.5	—	0.18	—	4.7	—	0.044	—	1.4	—
Grand Mean			0.33	0.16	10.9	5.6	0.24	0.14	7.8	3.8	0.042	0.016	1.5	0.7

AORTIC SAMPLES

I. *Normal aortic tissue*—It will be seen from the data recorded in table 1 that the adenylpyrophosphatase activity of the normal aortic tissue usually was found to be moderately higher than the inorganic pyrophosphatase activity, the mean values for the two enzymes, expressed as the quantities of orthophosphate liberated, being, respectively, 0.21 and 0.16 mM/Gm. wet tissue/hour. Some tendency was noted for both the pyrophosphatase activities to increase in the 10-29-year age groups, but the number of samples available from subjects in this age range was too small to permit conclusions with regard to that point. No significant changes in the enzyme activities with age were found for the samples from the 30-85-year-old individuals. The activity values expressed on the basis of the tissue nitrogen content in general paralleled the values calculated on the basis of the wet tissue weight.

In contrast to the two pyrophosphatases the mean phosphomonoesterase activity of samples from children aged 0-9 years was found to be definitely lower (0.025 mM PO_4 lib./Gm. wet tissue/hour) than the average activity of samples from adults (0.046 mM PO_4 lib./Gm. wet tissue/hour). This difference is also apparent when the values are expressed on the basis of the tissue nitrogen content.

II. *Arteriosclerotic aortic tissue*—The mean phosphatase activities of arteriosclerotic aortic tissue portions have likewise been listed in table 1. Because of the possibility of the existence of a correlation between the degree of calcification present in the arteriosclerotic samples and the enzyme activities, an examination of such relationship was made in which the inorganic phosphate content of the samples served as a measure of the degree of calcification. As seen from table 2 the adenylpyrophosphatase and inorganic pyrophosphatase activities of the arteriosclerotic samples showed only moderate variations within the tissue phosphate range of 0.1-2.0%, whereas definitely lower values were observed for samples having a phosphate content between 2.0 and 7.0%. No certain decrease was noted in the phosphomonoesterase activity of the latter samples when the average value was calculated on the basis of the tissue nitrogen content.

Because the degree of calcification above a certain level seemed to have a definite influence on the activities of adenylpyrophosphatase and inorganic pyrophosphatase, comparison of the enzyme activities of normal and arteriosclerotic tissue portions of the same blood vessels was made separately on samples in which the arteriosclerotic tissue possessed a phosphate concentration below and above 2.0%. The results of the comparisons made on samples with a lower degree of calcification are shown in table 3. It will be seen from the data that the mean activities of adenylpyrophosphatase and inorganic pyrophosphatase, when calculated for the total number of samples, were moderately

TABLE 2. RELATIONSHIP BETWEEN TISSUE CONTENT OF INORGANIC PHOSPHATE AND PHOSPHATASE ACTIVITIES OF ARTERIOSCLEROTIC AORTIC AND CORONARY ARTERY SAMPLES.

Phosphate (PO_4) Concentration % of Wet Tissue	N	Adenylpyrophosphatase		Inorganic Pyrophosphatase		Phosphomonoesterase	
		mM PO_4 lib./Gm. Wet Tissue/Hour	mM PO_4 lib./Gm. Tissue N/Hour	mM PO_4 lib./Gm. Wet Tissue/Hour	mM PO_4 lib./Gm. Tissue N/Hour	mM PO_4 lib./Gm. Wet Tissue/Hour	mM PO_4 lib./Gm. Tissue N/Hour
Arteriosclerotic Aortic Samples							
0.10 - 0.29	10	0.17	4.2	0.18	4.8	0.041	1.1
0.30 - 0.69	35	0.18	5.1	0.14	4.0	0.047	1.4
0.70 - 0.99	5	0.15	6.4	0.13	4.0	0 036	1.2
1.00 - 1.99	2	0.12	3.2	0.14	3.9	0.037	1.0
Above 2.00	5	0.07	2.0	0.04	1.2	0.025	1.1
Arteriosclerotic Coronary Artery Samples							
0.10 - 0.29	16	0.39	13.3	0.35	11.3	0.044	1.5
0.30 - 0.69	8	0.39	12.9	0.19	6.1	0.049	1.6
0.70 - 0.99	4	0.39	13.3	0.21	7.3	0.046	1.9
1.00 - 1.99	7	0.32	11.0	0.22	7.7	0.037	1.4
Above 2.00	10	0.11	2.1	0.15	4.4	0.035	1.0

TABLE 3. MEAN ENZYME ACTIVITIES OF ARTERIOSCLEROTIC TISSUE EXPRESSED IN PERCENTAGE OF ACTIVITIES OF NORMAL TISSUE OF THE SAME ARTERIAL SAMPLES.*

Age Group (Years)	N	Adenylpyrophosphatase				Inorganic Pyrophosphatase				Phosphomonoesterase			
		Wet Tissue		Tissue Nitrogen		Wet Tissue		Tissue Nitrogen		Wet Tissue		Tissue Nitrogen	
		%	t of diff.	%	t of diff.	%	t of diff.	%	t of diff.	%	t of diff.	%	t of diff.
Aortic Samples													
30 - 49	15	92	1.13	94	0.89	88	2.74	89	2.25	87	2.35	86	2.10
50 - 59	19	86	2.94	91	1.70	90	1.60	95	0.68	104	0.47	113	1.21
60 - 75	19	77	2.07	76	2.48	86	1.59	91	1.26	95	1.26	96	0.55
30 - 75	53	85	3.32	86	3.04	88	3.42	91	2.11	95	0.96	98	0.30
Coronary Artery Samples													
30 - 75	24	80	2.85	93	0.80	81	3.22	89	1.10	127	3.36	135	2.30

* Arteriosclerotic samples with a high degree of calcification (tissue inorganic PO_4 content above 2.0%) are not included.

but significantly lower in the arteriosclerotic tissue sections than in the normal aortic tissue, both when expressed on the basis of wet tissue weight and tissue nitrogen content. In contrast to this, no certain differences were observed between the average phosphomonoesterase activities of the arteriosclerotic and normal tissue portions.

The arteriosclerotic aortic samples which possessed a tissue phosphate concentration above 2.0% were found to have markedly lower pyrophosphatase activities than the normal aortic tissue, the mean values for the adenylpyrophosphatase being 35% (wet tissue weight) and 37% (tissue nitrogen content), and for the inorganic pyrophosphatase 35% (wet tissue weight) and 38% (tissue nitrogen content) of the activities of the normal tissue. The corresponding percentage values for the phosphomonoesterase were 58 and 74.

PULMONARY ARTERY SAMPLES

The adenylpyrophosphatase and inorganic pyrophosphatase activities of the pulmonary artery samples were found to be moderately higher (average values, respectively, 0.25 and 0.20 mM/Gm. wet tissue/hour) than the corresponding activities of normal aortic tissue (table 1). In contrast to this, the mean phosphomonoesterase activity of the pulmonary artery tissue (0.032 mM/Gm. wet tissue/hour) was somewhat lower than the activity exhibited by the aorta. In accordance with the observations on aortic tissue the average phosphomonoesterase activity of pulmonary artery samples from children was found to be lower than the mean activity recorded for samples from adults.

CORONARY ARTERY SAMPLES

I. *Normal coronary artery tissue*—The results of the enzyme activity measurements carried out on the coronary artery samples are included in table 1. The recorded values show that the mean adenylpyrophosphatase activity (0.43 mM/Gm. wet tissue/hour) and the average inorganic pyrophosphatase activity (0.32 mM/Gm. wet tissue/hour) of the normal coronary artery tissue are approximately twice as high as the activities of the aortic samples, whereas the phosphomonoesterase value (0.032 mM/Gm. wet tissue/hour) is of the same order of magnitude. The number of samples obtained from children and from subjects above 70 years was too small to permit comparison with values observed for persons aged 20-65 years. For the latter age group no significant changes in the phosphatase activities were observed with age.

II. *Arteriosclerotic coronary artery tissue*—As seen from table 2 a relationship was found between the inorganic phosphate content of the arteriosclerotic coronary artery samples and the enzyme activities which was essentially similar to that reported for the aortic samples.

The results of comparisons of the enzyme activities of normal and arteriosclerotic sections of the same coronary arteries are listed in table 3, which includes only observations on those samples in which a phosphate content below 2.0% was recorded for the arteriosclerotic portion of the vessels. It will be seen from the table that a decreased activity of both adenylpyrophosphatase and inorganic pyrophosphatase was found for the arteriosclerotic tissue, an observation similar to that made for the aortic samples. For the coronary artery samples, however, the differences were not statistically significant when calculated on the basis of the tissue nitrogen content. In contrast to the aortic samples the mean phosphomonoesterase activity of the arteriosclerotic coronary artery tissue sections was found to be significantly higher than the activity of the normal tissue.

The arteriosclerotic coronary artery samples which had a tissue phosphate content above 2.0% showed a further decrease in the pyrophosphatase activities as compared with the normal tissue. The mean percentage values for adenylpyrophosphatase and inorganic pyrophosphatase were 55 and 68, when calculated on the basis of wet tissue weight, and 51 and 88, when expressed on the basis of the tissue nitrogen content. The corresponding values for the phosphomonoesterase were 124 and 100%.

DISCUSSION

The present investigation has confirmed the findings by Baló, Banga, and Josepovits (3), Banga and Nowotny (4), and Antonini and Weber (2) of a high adenylpyrophosphatase activity in human arterial tissue. The recorded activity values for this enzyme in aortic tissue are somewhat higher than those listed by the previous investigators, a fact which may be due to the different experimental conditions employed and the larger number of arterial samples examined. In agreement with the observations by Banga and Nowotny (5) and by Antonini and Weber (2) the adenylpyrophosphatase activity of arteriosclerotic aortic tissue portions was in general found to be lower than the activity of the normal tissue.

The different pH optima and magnesium requirements demonstrated in the present study for the hydrolysis of adenosinetriphosphate and inorganic pyrophosphate tend to indicate that these activities represent the functions of two separate enzymes. For further elucidation of this subject investigations aimed at isolating the enzymes from the arterial tissue would be desirable.

The high adenylpyrophosphatase activity of human arterial tissue deserves attention since this activity represents an energy-producing mechanism. The fact that the activity of the enzyme in human arteries is of the same order of magnitude as in striated muscle tissue (4) is somewhat remarkable in view of the low oxidative metabolism of the arterial tissue.

SUMMARY

Determinations were made of the adenylpyrophosphatase, inorganic pyrophosphatase, and phosphomonoesterase activities of 86 samples of the aorta, 81 samples of the pulmonary artery, and 50 samples of the coronary artery obtained from individuals of various ages. In the case of the aortic and coronary artery samples the enzyme activity measurements were made separately on normal and arteriosclerotic portions of the same blood vessels.

The average enzyme activities of the normal aortic tissue, expressed as millimoles of PO_4 liberated/Gm. wet tissue/hour, were: adenylpyrophosphatase, 0.21; inorganic pyrophosphatase, 0.16; and phosphomonoesterase, 0.041. The corresponding values for the pulmonary artery tissue were 0.25, 0.20, and 0.032; and for the normal coronary artery tissue 0.43, 0.34, and 0.032. The phosphomonoesterase activity of samples from children was lower than the activity observed for adult tissue; in the case of the pyrophosphatases no certain change in enzyme activity with age was found.

The mean adenylpyrophosphatase and inorganic pyrophosphatase activities of the arteriosclerotic aortic and coronary artery tissue were moderately lower than the activities of the normal tissue of the same arteries. In contrast to this, no significant difference was observed between the phosphomonoesterase activity of the arteriosclerotic and normal aortic tissue and a higher average phosphomonoesterase activity was recorded for the arteriosclerotic coronary artery tissue as compared with the normal tissue.

Observations on the pH and magnesium dependency of the adenylpyrophosphatase and inorganic pyrophosphatase activities of the arterial tissue tend to suggest that these activities represent the functions of two different enzymes.

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CHANGES IN CENTRAL PULSE AND FINGER PLETHYSMOGRAPHY DURING AGING

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Records of the carotid or finger pulse can be made without discomfort to the subject. For this reason they can be expected to represent cardiovascular events occurring normally. They may not depict these events with great accuracy, but many of the changes occurring during aging can be easily observed. The results to be reported here parallel those obtained by using more accurate methods.

METHODS AND MATERIALS

For recording the carotid pulse we have used a glycerine pellet connected by tubing about 30 cm. long to a Grass strain gauge. For finger plethysmography, a finger cup was placed on a finger (usually the third) of one hand and volume recorded. A pressure cuff was placed on this finger close to the finger cuff. The recordings were amplified to the size required for accurate measurements of contour and timing. The paper speed for this work was either 50 or 100 mm./sec. The pressure in the cuff could be raised rapidly at any time in the cardiac cycle, by means of a solenoid switch activated after an appropriate delay by the subject's R wave. This switch opened a valve between the large pressure bottle and the pressure cuff. Usually the valve was caused to open about 0.1 sec. prior to the next systole, so that the artifact produced by the pressure cuff did not affect the recording of the next cycle. The records were obtained with the subject in a supine position and the fingers at approximately heart level. The vessels of the finger could usually distend enough following occlusion so that the normal inflow could be accommodated for 2, 3, or 4 successive beats. However, to be sure that no distortions resulted from a rise in venous pressure, we have measured only the first cycle, averaging the records from 8 to 10 venous occlusions.

As results accumulated, it became obvious that the contour of the peripheral pulse was different in older men than in younger individuals, and we, therefore, decided to see whether the carotid pulse showed similar changes. Although the purpose of this work was not to study pulse velocity, since we had records showing the difference in the time of arrival of the pulse at the carotid and at the finger, we are reporting these results.

These studies were made in an air-conditioned room which was maintained at a temperature of about 28 C. The temperature of the room varied about one degree from the mean. It always felt comfortable to the subjects. For analysis of our results the subjects were divided into those under 40 (19 subjects) and those over 50 years of age (18 subjects). The groups included about an equal number of each sex. We used the Student's t test for determining P value of the difference.

RESULTS AND DISCUSSION

On a few subjects, observations were repeated a week or more apart and on these subjects the results checked satisfactorily. For example, on one subject, the peripheral crest time was 0.218 sec. at one time and 0.228 sec. at another. The finger blood flow was observed to be 2.1 ml./10 ml. of finger vol./min. and 2.6 ml. on two different days.

Finger blood flow.—Finger blood flow as measured by plethysmography is dependent upon a number of factors. Those to be considered here are vasomotor changes, arterial and venous pressures, and age. Burch (1) has pointed out the importance of considering the α waves in measurement of blood flow. The increase in pulse volumes and increase in finger volume are correlated with vasodilation and small pulse volume and reduced finger volume with vasoconstriction. In some subjects these α waves are large and in others they are quite small. For our work we have made no attempt to record at any particular phase of the α waves, and have averaged the large and small flows recorded on each subject. The finger blood flow for those under 40 years (average age 26 years) averaged 4.77 ± 0.62 ml./10 ml. of finger vol./min. (table 1); for the group over

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TABLE 1. THE CHANGES WITH AGE OF CAROTID AND FINGER PULSE AND FINGER BLOOD FLOW.

	Finger Blood Flow in ml. /10 ml. of Finger Vol. / Min.	Finger Pulse vol./10 ml. of Finger Volume	Carotid Pulse		Finger Pulse	
			Crest Time	Half Amplitude Time	Crest Time	Half Amplitude Time
Younger Group (less than 40 years)	4.77 ± 0.62*	0.64 ± 0.07	0.130 ± 0.007	0.053 ± 0.015	0.163 ± 0.006	0.067 ± 0.002
Older Group (over 50 years)	2.76 ± 0.19	0.54 ± 0.03	0.175 ± 0.014	0.056 ± 0.032	0.228 ± 0.006	0.089 ± 0.003

* Standard error of the mean.

50 (average age 59 years) the figure was 2.76 ±0.19. The *P* for this difference is <0.01.

Brandfonbrener and associates (2) have shown that the cardiac output decreases about 1% per year during adult life. Our observations based on finger volume suggest that the blood flow in this region diminishes even more rapidly than heart output during aging. Since the systolic and diastolic pressures are about the same for the two groups, the reduced flow must have resulted from increased resistance in the fingers. An increase in whole body resistance during aging has been reported by Landowne and associates (4).

With each pulse the finger expands. For the younger group this expansion was 0.64 ± 0.07 ml./10 ml. of finger volume and for the older group the figure was 0.54 ± 0.03. The difference is not statistically significant.

Pulse crest time.—In these observations we have studied the crest time (foot to peak time) for carotid and finger pulses. For both central and peripheral pulse, there is a lengthening of crest time with age. This may be recorded as a fraction of a second or as a proportion of the total cycle. The results are similar in either case. A lengthening in the crest time in the toe pulse during aging was observed by Simonson (5), who found this to average 0.138 sec. for a group of 18 to 27-year-old men and 0.149 for a group between 45 and 54 years. Our results, which include both sexes, averaged for finger pulse of the group under 40 years (average age 26 years) 0.163 ± 0.006 (table 1) and for the group over 50 (average age 59 years) it was 0.228 ± 0.006. *P* was <0.01. Our results show the same trend as Simonson's but with a larger difference in crest time. Simonson's results were obtained using a photoelectric plethysmograph on the toe while we used the usual finger plethysmograph. His observations were all made on men only while ours included both sexes. For his analysis he divided his observations into those obtained from subjects 18 to 27 years of age and those from the group 45 to 54 years old while our results included a wider spread in age. If we select from our results only those from the subjects who were 18 to 27 years old, the crest time averages 0.134 sec., a result similar to Simonson's, but for our group 45 to 54 years old the average is found to be 0.174 sec., considerably higher than his results.

The crest time for carotid as well as the finger pulse was lengthened with increasing age. In the younger group it was 0.130 ± 0.007 second and the older group 0.175 ± 0.014. The *P* value for the difference is <0.01. The lengthening of crest time of the carotid pulse suggests a slowing of the cardiac ejection during aging, a conclusion reached by Starr and associates (6) as a result of observations with a ballistocardiograph. The explanation for the fact that crest time is longer in the peripheral pulse than in the central pulse has been discussed by Hamilton and associates (3).

Contour of rising limb pulse record.—We have been interested not only in the crest time of these pulses but also in the shape of the rising limb. If one measures the time required to reach half of the crest amplitude, then one obtains the following results: for carotid pulse the figures for the younger group averaged 0.053 ± 0.015 (table 1) and the older group 0.056 ± 0.032. In other words, in systole the carotid artery starts to expand rapidly in the younger group and continues this rapid expansion. In the older group, the expansion also begins rapidly but soon slows. On the other hand the finger vessels of the older group expand more slowly throughout systole. For the younger group, the time required for finger

pulse to reach half of the crest time amplitude was 0.067 ± 0.02 and for the older group 0.099 ± 0.003. The *P* for the difference is <0.01. In order to see how the contour of the rising limb in the finger pulse changes with age one can divide the time required to reach half of the crest amplitude by the crest time. By expressing the results in this manner, we arrive at the same values for younger and older groups, 0.41. Therefore, one can conclude that aging tends to reduce the slope of only the last part of the rising limb of the central pulse but slows the entire rising limb of the peripheral pulse.

Pulse velocity.—By making suitable correction for the time required for the pulse to travel up the carotid rather than out the aorta and subclavian, our results can be used to calculate pulse velocity from aorta to finger. We have subtracted 10% of the time difference to correct for this factor. Realizing that the diastolic pressure should affect pulse velocity, we separated our subjects into those with diastolic pressures under 75 mm. Hg and those over 75. Those with diastolic pressures under 75 mm. had a pulse velocity of 9.5 ± 0.36 mm./sec.; for those over 75 mm. the average was 10.1 ± 0.21 mm./sec. If one now divides the group with diastolic pressure under 75 into older and younger subjects, then the velocity seems to be the same in both groups, although we have too few observations. Since these results represent the velocity over large and small vessels, they are not comparable with results reported by other workers.

SUMMARY

Blood flow in the finger of subjects in a comfortably warm room (28 C.) averaged for the younger group (under 40) 4.77 ± 0.62 ml./10 ml. finger vol./min. and for the older group (over 50) 2.76 ± 0.19 ml.

The crest time (foot to peak time) for the carotid pulse was for the younger group 0.130 ± 0.007 sec. and for the older group 0.175 ± 0.014 sec. For the finger pulse the crest times were 0.163 ± 0.006 and 0.228 ± 0.006 for the younger and older age groups, respectively.

In the younger group of subjects, the curves representing the expansion of the carotid artery and finger during systole have similar contours although the duration of the rising limb of the finger pulse is longer.

In older subjects, the expansion of the carotid artery during systole commences rapidly and then slows, whereas the finger pulse shows a slow but rather constant expansion throughout systole.

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ERRATA

In table 1 of the paper by Alex Comfort, The Longevity and Mortality of Thoroughbred Stallions (Journal of Gertontology, vol. *14:* 9-10) the value of q_x for 8 years of age in the right-hand half of this table should be .0357 instead of .3570 and the values of L_x for years 8 and 9 should be .9740 and .9392, not 1,0000 and .9740 as shown.

BOOK REVIEWS

THE EFFECT OF ADVANCING AGE ON THE HUMAN SPINAL CORD, by L. Raymond Morrison, with the collaboration of Stanley Cobb and Walter Bauer, published for the Commonwealth Fund by Harvard University Press, Cambridge, 1959, 127 pages, $6.00.

This book presents for the first time a description and an atlas of the human spinal cord at different ages, presenting data on cords from each decade of life up to and including the ninth. The need for this study actually arose from the research of the Arthritis Unit at the Massachusetts General Hospital, for it became obvious that basic control material was needed for comparison with the pathological specimens. The book consists of two parts, Part 1 being the histological description of the cord in the different decades of life and Part 2, the Atlas, presenting topographical sections of the segments of the spinal cord of one individual. The cords discussed in Part 1 are described as from autopsies from cases with no neurological symptoms.

Thirty-one cords were studied. Gross inspection was followed by fixation in appropriate solutions for frozen sections, celloidin, or paraffin embedding (the last being used only for Bodian preparations). A variety of stains, including those for axons, myelin, fat, elastic tissue, and neuroglia were used.

The cords of the second and third decades are described *in detail* rather than simply as "young" or "normal." In the older of these cases some changes are seen, including beginning pigmentation of nerve cells, some chromatolysis, and slight accumulation of fat. The neuroglia show mild degrees of hyperplasia in all except an 11-year-old subject.

Detailed descriptions of each succeeding decade present a rather consistent picture of accentuation of the changes. Even in the fifth decade the anterior horn cells are described as "entirely free from alterations" in only 1 out of 6 cases. Loss of cells is indicated by the presence of "empty cell spaces," occurring without glial activity. One case showed marked axonal reaction, with generalized chromatolysis and vacuolation of nerve cells. Perivascular fat-laden gitter cells are scattered through all columns of the cord at all levels in this decade.

In the sixth decade slight thickening of the pia-arachnoid, perivascular infiltration with lymphocytes and plasma cells, and the appearance of corpora amylacea around the edges of the cord are seen. Nerve cell changes are accentuated.

In the seventh decade thickening of meninges, including the dura, is observed. Pigment is now so abundant as to cause bulging and distortion of the nerve cells in most cases.

In the eighth decade nerve cells of the anterior horn are either shrunken or are swollen with pigment in all cases. Again, cell loss is seen without neuronophagia.

It is somewhat disappointing to find only one case given for the ninth decade. The lipochrome pigment, sometimes vacuolated, is very abundant, but while chromatolysis is seen in some parts of the cord, the anterior horn cells are hyperchromatic.

These somewhat varied descriptions of the cord, as the authors state in the Discussion, lead to a conclusion that "—abrupt generalizations are impossible;" but they also say "—a framework of order can be made out in which the degree of pathological variation can be, at least partly, correlated with advancing age."

The Atlas gives pictures of a "normal spinal cord" from a person aged 24 years, with cell counts of the various columns in order to give "at least an approximation to a quantitative method for the estimation of the 'dropping out of nerve cells' in various pathological conditions."

The type of descriptive analysis given in this book probably will seem far from the objectivity of exact detail which can be obtained in some fields of science; yet it does constitute a very real contribution to a field which has been little investigated. The authors' analysis of the cellular reactions at the end of Part 1 and the general conclusions to be drawn from them are particularly good.

The bibliography, while including a number of the classical papers on the spinal cord, is somewhat lacking in references to the very important papers on the general problem of age changes in the nervous system of more recent times, such as those of Oskar and Cecile Vogt.

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BREAST CANCER, The Second Biennial Louisiana Cancer Conference, edited by Albert Segaloff, C. V. Mosby Co., St. Louis, 1958. 257 pages, $5.00.

Almost any volume dealing with cancer can be expected to contain material of interest and relevancy to gerontology. In the present state of infancy of the latter, it is not always possible to distinguish pure aging phenomena from biologic processes which, although not directly senescent in origin, nevertheless have an important relationship to aging. Breast cancer is so related in several aspects which are discussed in this volume. Thus epidemiological data which are presented show, in the over-all, a progressively increasing incidence and death rate with advancing age. However, there are two contrasting phases in this regard; age specific rates in several major countries show an increasing mortality from breast cancer below age 50 and a decreasing trend after age 50. This observation is consistent with numerous others on the relation of the biologic activity of cancer to the age of the patient, in that it is now recognized that cancer in aged individuals tends to run a more benign (prolonged) course than in younger patients. Considerations regarding the response to castration and hormone therapy of breast cancer also relate to patient age in that breast cancer in the premenopausal patient often involves the use of castration and androgen therapy (estrogen is contraindicated), whereas in patients long past the menopause estrogens are often employed therapeutically.

The presentations and comments of 30 participants are incorporated in this volume. Included are surgeons, radiologists, pathologists, biochemists, endocrinologists,

chemotherapeutists, a psychiatrist, and an epidemiologist. The presentation consists of two sections on Basic Biology, a section on Definitive Therapy (Surgical and Radiologic), and one on Hormonal Therapy. Each section is followed by questions and answers, so that to some extent the atmosphere of the original conference is recaptured. Within the sections the presentation does not always follow the section designation. Thus in Basic Biology I there is an excellent presentation by Dr. Harley Shands, a psychiatrist, on the care of the terminally ill patient. One can readily understand the difficulty of the editor in properly placing this subject, since, in this instance, the analysis deals more with the attitude of the physician toward the terminally ill patient than with the patient's disease. Similarly mistitled is Basic Biology II which consists, in toto, of presentations dealing with therapeutic aspects of the problem.

It is the opinion of this reviewer that the conference contains much material of interest to the pathologist, radiologist, surgeon, and chemotherapeutist. Despite the fact that two sections bear the designation Basic Biology, there is only limited material of interest to the cancer researcher. The most intriguing report dealing with basic biology is that of Dr. Ian Macdonald, a surgeon, who discusses predeterminism in human cancer of the breast. He shows that histologic variants of favorable significance, both of ductal and lobular origin, amount to almost 20% of all cases and are largely responsible for the numerically comparable fraction of low malignant potential by other criteria. At the other extreme are histologic features of lethal significance, as in the so-called inflammatory or acute carcinomas which account for about 4% of cases. The remainder (approximately three-fourths of cases) for the most part, fall into the so-called sclerosing types, usually ductal in origin, which give no histologic clues as to biologic behavior.

Between the lines one can read of the evident frustration of the clinical scientists, who seem to have reached the end of their potential for dealing with this problem. Thus the pathologist confesses that, even from a prognostic point of view, what he can offer is limited. The surgeon admits that, in order to justify the use of mutilating radical mammectomy and to show convincing therapeutic results, he must exercise great selectivity in the choice of cases. Much of what the radiologist and chemotherapeutist accomplish is of a palliative nature. It is amply evident that a new approach to the problem is urgently needed, both from an understanding of the basic biology as well as therapy.

Such new approaches are much more likely to come from the basic researcher than from the clinical investigator dealing solely with the human disease. Much could have been gained in this conference by a larger representation of work going on in basic biology. There is overly much discussion of hormones in therapy, but strangely absent is a presentation and discussion of the stages of dependency and autonomy of hormonally produced tumors as shown by Furth in recent years. And one misses reference to the contributions of such giants in this field as Leo Loeb and Lacassagne. In short the rapport which must exist between basic and applied medical science is absent. Nevertheless, the volume contains an excellent distillation of what is currently known about human breast cancer as well as related controversial matter in the field of therapy.

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The Jewish Hospital, St. Louis

SÉNESCENCE ET SÉNILITÉ, by F. Bourlière. G. Doin et Cie., Paris, 1958, 110 pages, $2.94 (1500 French fr.).

The leading French gerontologist, Professor François Bourlière, Director of the *Centre de Gérontologie* in Paris, has written this very informative booklet on senescence and senility. The text, although remarkably concise, is full of factual details and represents an up-to-date survey of the subject.

It is published in a series of monographs on therapy. The author has to be credited for having devoted more than half of it to basic scientific information. This implies a commendable approach to therapy which is not always encountered in similar publications.

The chapters on the hygiene of aging and on the various therapeutic possibilities conclude this valuable addition to gerontologic and geriatric literature, where the reader will enjoy the combination of analytical precision and synthetical ability.

The bibliography gives due consideration to American as well as to European authors.

R. SCHAUS, M.D.
Luxembourg

METABOLISM OF LIPIDS, *British Medical Bulletin* (vol. 14, no. 3, Sept., 1958), Medical Department, The British Council, 65 Davies St., London, W. 1, pp. 197-278, $3.25.

This issue of the British Medical Bulletin contains 12 papers by British scientists dealing with various aspects of lipid metabolism. The presentation in all the chapters is unusually clear and concise, and the expressed opinions conservative and logical. This collection of papers can be greatly recommended to research workers dealing directly or indirectly with problems related to lipid metabolism and the pathogenesis of atherosclerosis. In view of the recent rapid developments in this field of biochemistry, the publication of the review is especially welcomed because it affords a valuable opportunity for the reader to acquaint himself with the current stage of knowledge.

J. E. Kirk, M.D.
St. Louis

PROCEEDINGS OF SEMINARS; 1957-1958. DUKE UNIVERSITY COUNCIL ON GERONTOLOGY. E. Busse (Chairman), edited by F. C. Jeffers, Durham, N. C., 1958, 90 pages, $1.00.

This volume contains reports of 8 research seminars held at Duke University under the sponsorship of the Duke University Council on Gerontology. The topics covered by guest speakers include Biological Aspects of Aging (A. I. Lansing), Radiation, Aging and the Nervous System (H. F. Harlow), Arteriosclerosis (O. J. Pollak), Medical Genetics (A. I. Chernoff), Learning (H. Kay), Social Competence (R. J. Havighurst), Longitudinal Studies on Retirement (G. F. Streib) and Gerontological Research in the Netherlands (R. J. van Zonneveld). Although some of the presentations deal

with specific research problems, the volume is valuable in offering the points of view of various speakers. As a demonstration of what can be gained from a research seminar approach to the complex problems of aging, this book must be acclaimed a success, even though the recorded discussion is somewhat sketchy. The book will serve a useful purpose for all workers in gerontology.

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THE CARE OF THE GERIATRIC PATIENT, edited by E. V. Cowdry, C. V. Mosby Co., St. Louis, 1958, 438 pages, $8.00.

Here is a small, attractive, useful book, edited by E. V. Cowdry. An earlier work on Problems of Aging by the same editor, which appeared in 1939, offered a summary of information principally on basic data. The present work of 438 pages of fact-packed information concentrates at the clinical level. The appearance of this volume is timely.

Dr. Cowdry used the occasion of a Symposium on Care of the Geriatric Patient in the summer of 1955, under the auspices of the Los Angeles County Medical Society, to utilize 5 presentations of that Symposium as the first 5 chapters of the present volume. Fourteen more chapters have been added. Topics chosen for discussion adhere to the immediate issues of the broad field of human aging. Each presentation is the carefully reasoned résumé of a special area by an authority. The series of discussions, accordingly, represents a summary of the best current clinical thinking.

The opening chapter by Dr. Cowdry on The Physician and the Geriatric Patient, orients the medical practitioner concerning his responsibility for medical service to the elderly. Cowdry emphasizes the common sense point of view which reveals geriatrics as the general practice of medicine with older patients similar to the practice of pediatrics with children as patients. The difference, however, is the absence of long years in the trials and tribulations of living which are the sum total of the older patient's content. The formula for service, which Cowdry recommends, is attractive in many ways. Best of all, perhaps, is the rapid development of a new dimension dealing with the elderly individual. New knowledge is accumulating concerning the health and well-being of older individuals.

A review of the contributors reads like a Who's-Who list selected from the authorities of the field. Certain chapters are particularly commendable. Wilma Donahue has reviewed the Psychologic Aspects in the Management of the Geriatric Patient in admirable fashion. The chapter on Surgical Aspects of Geriatric Care by Louis M. Orr maintains the quality of the other chapters. In his discourse on the biliary tract, a number of surgeons would not agree with his statement that perforation of the gallbladder is as likely to occur as perforation of the appendix. Dr. Orr's emphasis on prompt ambulation is well placed.

Chapter 6 on Anesthesia for the Aged by Paul H. Lorhan is the best summary this reviewer has read. It is a splendid review of current thought concerning the management of anesthesia in the elderly patient. Dental care by Edward F. Allen is another highlight of the volume. Nursing Homes by Ollie A. Randall reviews the status of various types of facilities available, together with a listing of their shortcomings and indications for improvement.

The final chapter, Geriatrics Around the World, by J. H. Sheldon should be required reading for all medical students. It reflects the great interest in the health, medical, and social problems of the elderly in other nations throughout the world. Unfortunately, the majority of members of the medical and para-medical professions have hardly a passing acquaintance with the many programs directed to improving the lot of the aging and the aged. Yet this broadening subject contains within it material of first rate importance in the creation of a healthier, happier later life for older people.

This small, handy volume, published by Mosby, is highly recommended.

EDWARD L. BORTZ, M.D.
Philadelphia

BOOKS RECEIVED

Lebensdauer, Altern und Tod in der Natur und im Menschenleben, by Karl Friederichs, Vittorio Klostermann, Frankfurt am Main, 1959, 210 pages, DM 76.80, paper bound.

Metabolism of Lipids, British Medical Bulletin, vol. 14, no. 3, Sept., 1958, Medical Department, The British Council, 65 Davies St., London, W. 1, pp. 197-278, $3.25 (reviewed in this issue, page 193).

Proceedings of Seminars: 1957-1958, Duke University Council on Gerontology, E. Busse (Chairman), edited by F. C. Jeffers, Durham, N. C., 1958, 90 pages, $1.00 (reviewed in this issue, page 193).

Pulmonary Circulation. An International Symposium, 1958, sponsored by the Chicago Heart Association, edited by Wright R. Adams and Ilza Veith, Grune & Stratton, New York, 1959, 316 pages, $4.50.

Sénescence et Sénilité, by F. Bourlière, G. Doin et Cie., Paris, 1958, 110 pages (reviewed in this issue, page 193).

The Effect of Advancing Age upon the Human Spinal Cord, by L. Raymond Morrison, with the collaboration of Stanley Cobb and Walter Bauer, Harvard University Press, Cambridge, 1959, 127 pages, $6.00 (reviewed in this issue, page 192).

Verhandlungen der Deutschen Gesellschaft für Kreislauforschung, Band 24: Die Lebenswandlungen der Kreislauforgane in Abhängigkeit von Alter und Geschlecht, by Rudolph Thauer, Dr. Dietrich Steinkopff Verlag, Darmstadt, 1958, 386 pages, DM 50, paper bound.

JOURNAL OF GERONTOLOGY

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Section B

Psychological and Social Sciences, Social Welfare

Edited by

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VOLUME 14, SECTION B APRIL, 1959 NUMBER 2

THE WAIS PERFORMANCE OF AN AGED SAMPLE: THE RELATIONSHIP BETWEEN VERBAL AND PERFORMANCE IQs*

CARL EISDORFER, Ph.D., EWALD W. BUSSE, M.D., AND LOUIS D. COHEN, Ph.D.
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The Wechsler Adult Intelligence Scale (WAIS) standardization for older people is based upon data collected from Metropolitan Kansas City (5). The sample and the testing procedures have been described by Doppelt and Wallace (1, 2). Although 659 persons were contacted and 475 tested, acceptable full-scale tests were administered to an N of only 352. Since the results obtained from this sample are proposed (although with some hesitance) by Wechsler as tentative national norms and are thus used, it becomes necessary to test the generality of these norms for other areas of the United States.

During the three years that the Duke Geriatrics Project has been functioning, intensive physical, social, psychiatric, and psychological examinations have been given to more than 200 aged, socially-functioning volunteers. A number of institutionalized aged have also been studied. Subjects for this project live in the Piedmont (Central) section of North Carolina and, for the most part, in the Durham, Chapel Hill, Raleigh triangle and its environs (an area of approximately 115 square miles).

It was noted quite early that these subjects exhibited superiority of Verbal over Performance IQs, and it was decided to investigate the consistency of this phenomenon. (We hope to publish at a later time our data on the WAIS Performance for our entire sample so that they may be compared with the Kansas City sample).

THE SAMPLE

All subjects were over 60 years of age and residing in the community at large. Volunteers were obtained through retired men's clubs, Golden Age societies, local industrial firms, medical societies, radio and television broadcasts, and through the volunteers themselves who were asked to contact acquaintances. All over 60 years of age who volunteered were accepted. Subjects for a special analysis were secured from the State Hospital at Butner, North Carolina.

One hundred and thirty subjects were used in this study. Divided according to the age groups utilized by Wechsler, there were 23 subjects aged 60–64; 38 subjects aged 65–69; 37 subjects aged 70–74; and 32 subjects aged 75 and above. There were 32 mental hospital patients in addition to these volunteers.

PROCEDURE

As a portion of the extensive examination procedure included in the Duke Project, a full scale test of intelligence is administered to each subject. (In the past this has been either the Wechsler Bellevue Form I [WBI] or the WAIS.) This test is administered during the first morning of a two-day examination period. All subjects seen from March, 1955, through February, 1957, who had received all subtests on the WAIS, were included in the present analysis. Only six subjects were eliminated for failure to complete all subtests; three because of uncorrected defective vision and three because of neurological handicaps.

This rather low rejection rate (5 per cent as compared with the 25 per cent of the Kansas City sample) may be a function of differences in motivation in the respective samples. Thus, while subjects in Kansas City were contacted directly and requested to volunteer for this study, those in the Piedmont sample were sufficiently motivated to request examination themselves.

The examinations were administered by two qualified psychologists. When the patterns of verbal and performance results obtained by these psychologists were compared, no signifi-

* This study was carried out with the support of the National Institute of Mental Health grant M900 C, Dr. Ewald W. Busse, Principal Investigator.

A modified version of this paper was delivered at the sixty-fifth annual meeting of the American Psychological Association, September, 1957.

cant differences between their results were noted (a chi-square test was applied).

For each subject, Scaled Scores, Verbal, Performance, and Full Scale IQs were computed, based on the standard procedure prescribed by Wechsler. The variables of sex, socio-economic status, race, high and low intelligence, and mental health status were considered in this study.

Sex, age, and race variables require no special definition. Socio-economic status was defined according to a dichotomy based on indices specified below. High and low intelligence were defined acording to a dichotomy based on the Full Scale IQ score, with an IQ of 100 as the dividing point. The mental health status variable, which involved the addition of 32 elderly mental hospital patients to this study, distinguished between mental hospital patient status and functioning community volunteer status.

Since the data utilized by Wechsler's standardization study are fitted to a normal distribution, the expectation for the superiority of Verbal or Performance IQ for any subject should be equal: that is to say, the probability value for either Verbal or Performance IQ to be superior is .5. This made it possible to analyze the incidence of Verbal IQ scores greater than Performance IQ scores for individual subjects through the use of a binomial expansion (3).

In order to compare further the subtest performance of the Piedmont and Kansas City samples, the mean of the raw scores for each subtest in each age group in the Piedmont sample was calculated. This value was then compared with the Tables of "Scaled Score Equivalents of Raw Scores" for the appropriate age groups, which are given in the WAIS manual (5). (In these Tables, which are based upon Wechsler's normative data, it is possible to convert a raw score into a weighted score appropriate for each age group.) This procedure allows direct comparison with the Kansas City data.

RESULTS

Table 1 presents the percentage of cases in the Piedmont sample in which (using conventional scoring methods) the Verbal IQ score was higher than the Performance IQ score.

For the Community Volunteer sample as a whole, Verbal IQ was higher than Performance IQ in 82 per cent of the cases. The probability level for this superiority of Verbal over Performance scores is beyond the .05 confidence interval as defined by the binomial expansion. This superiority is consistent and significant when the sample is divided by age, by sex, by race, by social class, by intelligence, and finally, by mental health status.

Figure 1 shows the performance of the Community Volunteer sample as a whole on each subtest with the results compared with the Kansas City norms. Perfect agreement between the results obtained from the Piedmont sample and the Kansas City sample would result in a straight line at the level of scaled score 10. The IQ scores at the right represent the mean IQs obtained in the usual manner, and demonstrate a "V" shape, with Verbal IQs higher than Performance IQs or Full Scale IQs. It is this superiority of Verbal to Performance score which is considered to be of particular interest. It can be seen, too, that Verbal IQ is somewhat higher than the norm. This may reflect a bias in our sample, since the sample includes thir-

TABLE 1. VERBAL IQ SCORES AND PERFORMANCE IQ SCORES FOR THE PIEDMONT SAMPLE.

Community Volunteer Sample (N = 130) grouped according to	N	Per cent with Verbal IQ higher than Performance IQ*
Age:		
60 - 64	23	91
65 - 69	38	84
70 - 74	37	76
75 and above	32	78
Sex:		
Male	65	85
Female	65	78
Race:		
Negro	26	77
White	104	83
Socio-economic Status:		
High	54	94
Low	76	72
High vs. Low IQ:		
Over 100	63	89
Under 100	67	75
Total Community Volunteer Sample	130	82
Mental Hospital Sample	32	91

Note.—IQs computed by conventional WAIS scoring method.
*All percentages significant at .05 level or beyond.

teen retired college professors in the Durham-Chapel Hill community.

In order to test the possibility that the results obtained in this study are artifacts of the sample, the data were re-analyzed according to the variables cited above. Figure 2 demonstrates that when subjects are grouped according to age and then according to social class, the results show a consistent pattern of superiority of verbal to performance scores. The criteria of Warner's "Index of Status Characteristics" (4) (*i.e.*, occupation, source of income, house type, and dwelling area) and level of education were used to categorize the volunteer subjects into the 8000 (high status) and 4000 (low status) socio-economic groups. Subjects in the 8000 group were at least high school graduates. They were practicing or retired professionals, businessmen, or farmers who owned their land and who employed two or more full-time employees. The 4000 group was chosen from those community volunteers who had only elementary school education. They were laborers or tenant farmers, or they subsisted on community welfare funds. Women were placed in the 8000 or 4000 group according to the data available on their husbands.

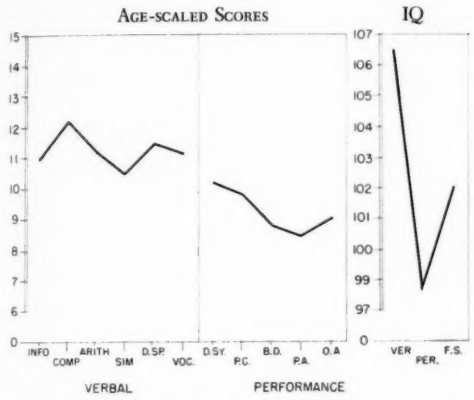

Fig. 1. Mean age-scaled scores for each subtest, mean Verbal IQ, mean Performance IQ, and Full Scale IQ on the WAIS for the Community Volunteer sample (N = 130). A score of 10 implies agreement with the Kansas City norms.

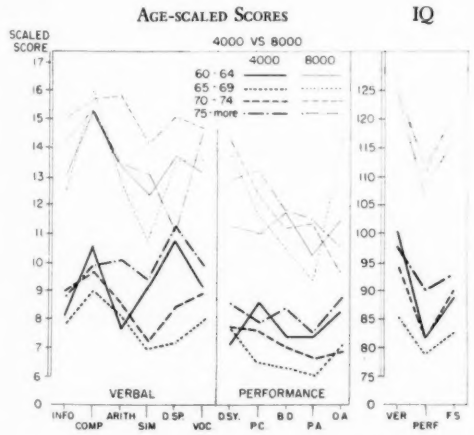

Fig. 2. Mean age-scaled scores of each subtest, mean Verbal IQ, mean Performance IQ, and Full Scale IQ on the WAIS for the Community Volunteer sample according to socio-economic status and age. Four thousand refers to low, and 8000 to high, socio-economic level. A score of 10 implies agreement with the Kansas City norms.

The findings in Figure 2 are consistent with those already reported. The graph on the right of the figure indicates that for all of the eight subgroups, Verbal IQ scores are well above Performance IQ scores.

Figure 3 shows the comparison between socially-functioning community volunteers (our Piedmont group) and the State Hospital sample (0500), both groups divided according to age. This figure shows the consistent superiority of the Verbal over the Performance subtests and

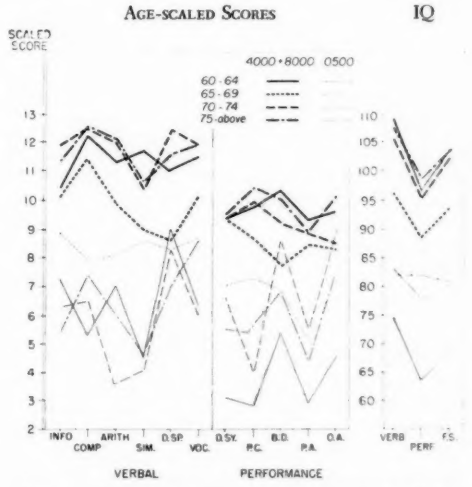

Fig. 3. Comparison between the Community Volunteer and the Mental Hospital samples on mean age-scaled scores for each subtest, mean Verbal IQ, mean Performance IQ, and Full Scale IQs. Four thousand refers to low, and 8000 to high, socio-economic status; 0500 refers to the State Hospital sample.

IQs. The 70–74-year-old patient group is the only group for which the Verbal IQ was not higher than the Performance IQ.

DISCUSSION

This study is concerned with the superiority of the Verbal over the Performance IQs in our Piedmont sample and has attempted to identify a number of variables which might account for this superiority. Our *a priori* assumptions led us to believe that differential life experiences would influence this relationship of scores. We therefore investigated certain factors which might be expected to contribute to different life experiences (*i.e.*, sex, race, socio-economic status, intelligence level, and mental health status). No matter which of these variables we examined, we noted the consistent superiority of the Verbal over the Performance IQs.

Our next assumption was that our Piedmont subjects might be a biased sample, selected so as to maximize the particular relationship noted. Examination of the selection process followed in this study indicates that in large measure the criterion influencing our selection was the availability of subjects. Subjects from the community at large were studied since we were interested in the normal process of aging. As soon as a substantial number of subjects were secured the population characteristics of Durham were studied, and subjects were solicited from among specialized groups so as to approximate the range of characteristics of the Durham census for age, sex, race, and geographic distribution. At the time of this analysis we had not as yet reproduced the Durham census distribution, but we had approximated it. All our subjects were ambulatory volunteers who were sufficiently motivated to come and be studied for two days. In addition, the Piedmont subjects received what might be considered a reward for their efforts as subjects in the Duke Geriatrics Project, *i.e.*, a full scale physical examination (and, for those who requested it, a summary of the findings forwarded to the family physician). This motivational (and reward) factor may have been involved in the reduced rate of rejections for failure to complete all of the WAIS sub-tests. That is to say, the Piedmont subjects may have been motivated to attempt all of the test items while many of the Kansas City subjects, lacking such motivation, may have "given up" when they were confronted with difficult performance items. This would result in an analysis based, to some extent, upon the results obtained from those Kansas City subjects who could function most adequately on these items. To this extent there is a population bias; but the extent to which this could influence the verbal/performance relationship is unknown.

One group of subjects, the hospitalized elderly who were able to complete the WAIS, were non-volunteers selected in serial order. These subjects demonstrated the same verbal/performance relationship noted earlier. Thus the fact that volunteers were used did not seem to account for the phenomenon noted.

We have been hard pressed to explain these results. There has been a suggestion that loading the sample with highly educated people would dispose to higher verbal than performance scores. The verbal/performance relationship is more marked (see Table 1) for the higher socio-economic status group (94 per cent, with Verbal IQ higher than Performance IQ) but there are still 72 per cent of the lower socio-economic status group with Verbal IQ higher than Performance IQ. This is true, even though 76 of 130 subjects are in the lower socio-economic status category.

It is true that the sample is limited in size, but it begins to approximate one half the subjects of the Kansas City standardization population. It was felt that the particular relationship between verbal and performance scores noted here was so unusual and so consistent that it warranted being reported. Additional data are being collected from our larger study to check these findings.

We may conclude that, for the sample under consideration, the population variables usually associated with variations in intelligence test scores have been investigated without revealing inconsistency in the pattern of superiority of Verbal IQ to Performance IQ. It is difficult to interpret these results except insofar as they represent a sample of a different population from that examined in Kansas City. Our findings raise some question concerning the generality of the norms obtained from a sample of aged subjects from one geographic area. One implication is that Wechsler's data must be supplemented by data drawn from various parts of the United States with a view toward reaffirming or modifying the WAIS norms for persons aged 60 and above.

SUMMARY

The WAIS standardization for older people was established on a Kansas City sample. The present report presents findings from another geographic region.

The WAIS records of 130 normal volunteer subjects aged 60 years and above living in the Piedmont section of North Carolina, and of 32 hospitalized patients, were studied for differences between verbal and performance scores. The Kansas City data, which serve as the WAIS norms for these age groups, were used as the criteria.

The Performance IQs and age-scaled scores were used in comparisons made for the entire normal sample. Further analysis with male or female sub-groups, white or Negro, high or low intelligence, better or poorer socio-economic status, and mental health status, revealed the same pattern.

These results appear to raise some question about the generality of the Kansas City sample when used as the basis for national norms.

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AGE AND THE EFFECT OF ANTICIPATORY SET ON ACCURACY OF PERCEPTION*

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Experimental research (6) has shown that the deterioration in performance which occurs with aging, though manifested in effector processes, is probably the result of changes in the central organizing functions of the nervous system. The diminished speed or accuracy observed in older people working on complex motor tasks has been attributed (1, 3) to a less efficient use of anticipatory sets, which are central processes. Anticipatory sets or expectancies act as selective agencies in determining the efficiency of performance in all cognitive tasks that require the sequential integration of acts, that call for rapid response, or that involve uncertainty because of the possession of more or less ambiguous information. Failure to use anticipatory sets could be caused either by incapacity to maintain an expectancy after its initial application, or by inability to formulate such an expectancy from the available cues. There is evidence (7) that, in senile dementia, defects in perceptual functioning can be attributed to an inability to use cues. Both the maintenance of a set and its original adoption can be hindered by the operation of a rival set. Perseveration occurs when a set is carried beyond its appropriateness to the task and prevents the adoption of the appropriate set. Expectancies, however, can also interfere with the effective use of another set before they cease to be appropriate, e.g., when two or more sets are disjunctively appropriate to the situation. For example, the tennis player, to return the service, must be ready either with forehand or backhand. The anticipatory adoption of one posture may pay off with a resounding drive; but, if the ball bounces on the unexpected side, the player is likely to lose the point.

The experimental study here reported was designed to determine whether healthy sexagenarians and septuagenarians are indeed less efficient in (a) continued application, (b) original formulation, and (c) alteration of anticipatory sets than are younger persons. The relative capacity to alter a set was tested both under conditions in which one expectancy ceased to be appropriate and under conditions in which more than one set could be appropriate.

METHOD

The experimental group was recruited from members of three Boston recreational and study clubs for the older age group. Nine men and nine women volunteered to act as subjects. They ranged from 65 to 75 years, with a mean of 70. All were in good health, and, though most of them were retired, they were active in the programs of their clubs. In this respect they undoubtedly formed an unrepresentative sample of their age group, biased in the direction of less-than-average senescence. It is also likely that they were unrepresentative with respect to past social responsibilities, experience, and intellectual standing, for most of the men and several of the women had been engaged in professional or in executive positions. Though not tested for IQ, all appeared to be of higher-than-average intelligence. Their English was fluent, and in each case English was their native language.

The control group was biased in much the same directions. It consisted of 27 men and 27 women who were members of the professional and clerical staff at the Massachusetts General Hospital or were enrolled in one of the training programs at that institution. Their ages ranged from 20 to 40, with a mean of 26.9 years.

The effect of anticipatory sets was tested by presenting auditory material (single words) for correct vocal reproduction at the threshold of intelligibility. The experiment consisted of a pilot list and eight test lists, varying in length between 12 and 36 words, some or all of which belonged to the same conceptual category, e.g., names of animals. All lists and preceding instructions were recorded on tapes. All were spoken by the same voice at a uniform level, except that the volume was set louder for the

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instructions. Silent intervals after each word were long enough for the subject to repeat the word aloud three times at the same pace. After the subject was seated comfortably, the experimenter instructed him to repeat in a clear, loud voice the words he would hear spoken on the tape recorder, though these would be only just intelligible and, in some instances, barely audible. The tape itself began with this instruction: "You will be hearing several lists of words. I shall read them just loud enough for you to hear me. Therefore you may not clearly understand *every* word you hear. Don't let that disturb you. Repeat out loud every word as it *sounds* to you." A pilot list of 24 words allowed the instrument to be set at the subject's individual threshold of intelligibility, i.e., at a level of volume and tone at which half the words were repeated correctly.

The test lists differed according to the conditions by which an expectancy was established, the manner in which it was confirmed, and the interference of a concurrent or preceding rival set. Expectancies can be created *explicitly*, e.g., by instructing the subject, "Now you will be hearing the names of animals." They can also be induced *implicitly*, by providing cues from which the subject can formulate an anticipatory set. In the present study the implicit set was created by prefacing the test list of 12 food names with a pilot list of six other food names. The instruction preceding a test of implicit set merely stated, "Now you will hear another list of words."

A set, once adopted, can be confirmed in every instance, partly confirmed, or entirely negated. One list testing the effect of *explicit* and one testing *implicit* sets furnished complete confirmation; i.e., they consisted of 12 words all of which represented the same conceptual category (names of animals or names of food). Two lists testing each of these sets carried partial confirmation; i.e., they consisted of 24 words only half of which were drawn from one category, while the other 12 each belonged to different categories. Some test lists given under *explicit* instruction were followed without break or warning by another list of words which were entirely (all 12) or partly (12 out of 24) drawn from one category, but a category different from that confirmed by the first list. The second lists tested the effect of a *counter set*, in other words, the interference of a set with the formulation of new expectancies.

Lastly, two test lists followed the instruction of a double expectancy: "Now you will be hearing names of birds and names of parts of the body." In one instance confirmation was complete, i.e., the test list consisted of 12 names of birds and 12 names of parts of the body. In the other instance confirmation was partial, i.e., twelve mixed words were scattered among the names of birds and names of body parts. In lists which consisted of words drawn from more than one category, no more than two words representing the same category or two mixed words followed in a run.

The design required 12 lists drawn from single categories and five lists of mixed words. The categories used were names of animals (A), birds (B), food (F), and parts of the body (P), each category providing three lists empirically matched for intelligibility. Names of animals were used to test single sets with complete confirmation; names of food, for single sets with partial confirmation; names of birds and names of parts of the body furnished double sets with both complete and partial confirmation. Each of the latter two also provided the single set interfering with the formulation of another set. Three tapes were recorded so that the same list of words appeared under different conditions of expectancy on each. The design of the experiment is set out in Table 1. Six experimental and 18 control subjects were tested on each of the three tapes. The tapes were divided into three sections of about equal length, as shown by the broken lines. To balance possible effects of fatigue, habituation, or test sophistication, a

TABLE 1. EXPERIMENTAL DESIGN.

Tape I	Tape II	Tape III
$\dot{A}_1$	$\dot{A}_2$	$\dot{A}_3$
$\bar{B}_1X_4{}^{\bullet}F_1X_1$	$\bar{B}_2X_4{}^{\bullet}F_2X_2$	$\bar{B}_3X_4{}^{\bullet}F_3X_3$
$\bar{F}_2X_3$	$\bar{F}_1X_1$	$\bar{F}_2X_2$
$\bar{B}_3\bar{P}_3X_5$	$\bar{B}_1\bar{P}_1X_5$	$\bar{B}_2\bar{P}_2X_5$
$\bar{A}_3$	$\bar{A}_1$	$\bar{A}_2$
$\bar{B}_2\bar{P}_2$	$\bar{B}_3\bar{P}_3$	$\bar{B}_1\bar{P}_1$
$\dot{F}_2X_2$	$\dot{F}_3X_3$	$\dot{F}_1X_1$
$\bar{P}_1{}^{\bullet}A_2$	$\bar{P}_2{}^{\bullet}A_3$	$\bar{P}_3{}^{\bullet}A_1$

Note.—A, B, P, and F symbolize the four classes of names, X the mixed words; subscripts stand for the number of the lists within each class (first, second, etc.); a line above a letter (e.g., $\bar{F}$) indicates an explicit set, a dot (e.g., $\dot{A}$) an implicit set, an asterisk (e.g., $\bar{P}{}^{\bullet}A$) the introduction of a list to which the previously-established expectancy is no longer appropriate.

third of the subjects assigned to each tape started with a different section.

Performance was scored under four headings: correct report; *assimilation*, or number of incorrect words congruent with an expectancy in operation ("hand" for "head"; or, as in the double expectancy situation, "toe" for "crow"); other incorrect words; no response. Differences between the mean number of correct reports by the two groups were tested by t ratio or, if variances were heterogeneous, by the Mosteller and Bush version of the Mann-Whitney test (2), which gives normal deviates (z scores). Probability of less than 1 per cent was taken as a statistical measure of significance.

RESULTS

The relative effect of one type of set or mode of confirmation was the same in both age groups. Whether confirmation was complete or partial, correct responses for *explicit* set and for the type of *implicit* set provided for by the experiment were not significantly different. Both explicit and implicit set made for significantly more correct responses than occurred when the test followed a previously confirmed and now inappropriate expectancy. With complete and partial confirmation alike, the scores were significantly lower under a double than under a single set. Under identical conditions of testing, names of parts of body were neither more nor less intelligible than those of animals or birds, and the latter were no different from names of food. Any list of twelve words drawn from one category gave a significantly higher mean score than the associated twelve mixed words, with the one exception of the test under conditions of counter sets. In the control group this difference was significantly large. However, both groups were alike in that correct reports congruent with the *minor* or less effective of two paired sets were still significantly higher than those for the associated mixed words.

Table 2 shows that, except in the case of the names of foods presented with partial confirmation and implicit single set, the control subjects reported more words correctly, no matter what the conditions of set and confirmation. However, the differences were significant only for either a double set or a counter set. Under those conditions the experimental group reported significantly fewer names correctly in accordance with either of the concurrent expectancies, for classified or for the accompanying mixed words.

In *assimilation* the two groups did not differ significantly in any of the test lists, and the ratio of errors of this type to all errors was exactly the same for both, .122. Assimilation formed a much larger proportion of errors made by incorrect response for the experimental group than for the control group, because the older persons were more inclined not to respond at all rather than risk an error. The mean ratio of no-response to total error was .73 for the experimental group, and .49 for the control group; and the t ratio for the difference is 4.90 ($p < .01$). Thus a difference in readiness to cope with uncertainty differentiated the two groups.

DISCUSSION

Under the conditions of this experiment, aging appeared not to diminish a person's capacity to maintain a single anticipatory set or to adopt an appropriate expectancy from the available cues. Neither did the two age groups studied differ in their dependence on consistent confirmation of their expectancies. For both alike, partial confirmation was as effective in maintaining a set as was complete confirmation. While the consistently lower scores of the experimental group might suggest that the absolute facilitating effect of expectancies decreases with age, their relative effect certainly does not uphold that conclusion. Both groups reported correctly more of the classified names than of the associated mixed words, even though the latter were not inherently less intelligible (4); and in each of the five instances the difference was larger, though not significantly so, in the experimental group. Therefore this experiment does not justify the opinion that older persons in general are more dependent than are younger persons on appropriate anticipatory sets for accurate performance.

Significant differences were found between the two groups in tests which involved a shifting from one set to another, either in rapid alteration or by abandoning an expectancy which was no longer appropriate in favor of another. It is questionable whether the relative deficiency observed in the older age group should be attributed to perseveration. Such a conclusion would no doubt suggest that one set prevailed at the expense of the other. This, however, was not the case. In both tests with a double set, the number of words reported cor-

TABLE 2. MEAN CORRECT RESPONSE ON TEST LISTS, AND ASSIMILATION AS PROPORTION OF TOTAL ERROR.

List and Mode of Presentation	Correct Responses				t Ratio ($\mathcal{S}$ Scores)	Ratio of Assimilated Errors to Total Errors	
	Experimental Group		Control Group				
	Mean Score	S. D.	Mean Score	S. D.		Experimental Group	Control Group
Classified Words							
Explicit single set:							
Complete confirmation: $\bar{A}$	8.61	1.61	9.24	1.35	1.62	.230	.174
Complete confirmation: $\bar{P}$	9.00	1.28	9.54	1.51	1.35	.296	.323
Partial confirmation: $\bar{B}$	8.28	1.84	9.37	1.58	2.39	.119	.140
Partial confirmation: $\bar{F}$	7.89	2.24	8.52	1.82	1.12	.149	.188
Implicit single set:							
Complete confirmation: $\dot{A}$	7.89	1.90	8.55	1.74	1.35	.108	.183
Partial confirmation: $\dot{F}$	8.44	2.12	8.17	2.26	.44	.281	.106
Explicit double set:							
Complete confirmation: $\bar{B}$	6.39	2.12	8.17	1.48	$\mathcal{S}$=3.00*	.089	.111
Complete confirmation: $\bar{P}$	6.00	3.14	8.06	1.87	$\mathcal{S}$=2.41*	.139	.183
Partial confirmation: $\bar{B}$	5.61	2.43	7.78	2.06	3.47*	.052	.128
Partial confirmation: $\bar{P}$	6.17	1.79	7.46	1.57	2.87*	.038	.118
Counter set:							
Complete confirmation: $*\bar{A}$	4.67	2.83	7.02	3.22	2.73*	.121	.249
Partial confirmation: $*\bar{F}$	4.67	3.50	7.02	2.46	3.09*	.023	.082
Mixed Words							
With explicit set: $\bar{X}_B$	2.11	2.24	3.65	2.46	2.30	.084	.169
With explicit set: $\bar{X}_F$	3.00	3.05	3.78	2.26	1.14	.092	.157
With implicit set: $\dot{X}_F$	4.06	2.67	4.80	2.11	1.18	.070	.118
With counter set: X_{*F}	2.50	2.62	5.55	1.71	5.58*	.035	.082
With double set: X_{BP}	2.94	2.56	5.48	2.10	4.10*	.166	.071

* Difference is significant with $p<.01$.

rectly with either set was larger than on any list of mixed words. This remains true when we take the experimental group's mean score on the less effective of the two joint sets.

In a study with patients suffering from Korsakoff's psychosis, in which a method very similar to that of the present experiment was used, Talland and Miller (5) also found that tasks requiring a double set differentiated experimental and control groups. However, those patients could effectively maintain only one of the two sets, their reports in accordance with the *minor* set being no better than that for mixed words. In this respect the experimental group of the present study did not differ from the control group; though the margin between correct reports congruent with the *major* and *minor* sets were wider in the older age group, the differences were not significant.

Neither did the assimilation data furnish evidence for the operation of a prepotent set or perseveration. In the tests with a double set, incidences of assimilation were evenly divided between the *major* and the *minor* set. Likewise, in the tests with a counter set, the few instances of assimilation were about equally split between

words with the first and with the second list of names.

An experiment (4) which served as a control for the present study suggested that anticipatory sets may operate as inhibitory rather than facilitating processes, by raising the thresholds for information that is not congruent with an expectancy. The differential performances of the two age groups here compared agree with that reasoning, and they would allow for its extension so as to attribute the effect of aging to an increase of this inhibitory potential. Only with a double set or a counter set did the experimental group correctly report significantly fewer of both classified and mixed words. This finding is consistent with an explanation that the differences between the two age groups result from an inhibitory effect rather than from a prolonged persistence of some active tendency.

It would thus appear that vigorous scanning or, at the observational level, flexibility in coping with alternative solutions or with conflicts between anticipation and event, deteriorates with age in the perceptual as well as in the motor processes. "Set rigidity" may perhaps describe most accurately the performance characteristic of the older age group, indicating a diminished capacity to change attitudes; but this set rigidity does not necessarily indicate perseveration. On the other hand, the results of this experiment should not be construed as demonstrating the absence of perseveration in the older age groups. The experiment was not designed to test the presence or absence of perseveration. Unlike disjunctive motor-reaction tasks, it did not limit the subject's response to a choice between a word from one class and from another; the subject could respond with any word he pleased or he could remain silent altogether.

One of the incidental findings of this study was the much stronger tendency shown by the older age group to keep silent rather than to give a wrong answer. Since the experimental conditions and instructions were the same for both groups, this difference can best be explained by attributing greater cautiousness to the older subjects. Doing so, however, need imply no generalization to a personality trait. Older people are indeed likely to be more cautious, thus offsetting precisely those disadvantages which occur with set rigidity. On the other hand, members of the experimental group in this study may merely have adopted a different attitude toward the testing situation from the attitude taken by the control subjects. After all, the experiment was designed to deceive the subjects. In some instances the words presented were congruent with that which the subjects had been led to expect; in other instances, the words sounded very different from that which they should have been, according to the instruction. Quite possibly the older subjects interpreted the experiment as a test of their sensory capacities, or for some other reason, were more anxious to avoid making mistakes. This attitude may account for their overall lower scores of correct response; but it does not account for the differential effects between single and double, direct and counter sets, which distinguished their performance from that of the control group.

SUMMARY

A group of men and women in the age range of 65-75 years was compared with a group aged 20-40 on a test of auditory perception. Lists of words were presented from a tape at each subject's threshold level of intelligibility, and his task was to repeat the words as he had heard them. Correct perception was facilitated by the operation of anticipatory sets, insofar as some of the words were drawn from the same conceptual category. No significant difference was found between the two groups in the facilitating effect of sets if all or part of the test words were drawn from one category. The effect of expectancy was reduced for the older age group if the test words could belong to either of two categories. The older age group was as capable as the younger in formulating an appropriate expectancy from cues provided, but less efficient than the younger if this formulation had to be made at the expense of another set which had previously been appropriate. However, the facilitating effect of an anticipatory set was in evidence under all test conditions in both groups. The findings are considered to be consistent with a view that changes in central inhibitory processes characterize normal aging and these changes are manifested in an increased set rigidity in cognitive as well as in motor performance.

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CROSS-SECTIONAL METHODS IN THE STUDY OF PSYCHOLOGICAL ASPECTS OF AGING

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Great emphasis has been placed upon the desirability of longitudinal studies in the field of adult behavior (1). This is not the place to examine fully the many problems inherent in the longitudinal approach. It should be pointed out, however, that while it is of great importance in the study of the single case, the longitudinal approach is in principle not amenable to some of the requirements of the experimental method. It is the cross-sectional approach which, in studying any postulated relationship, enables one to vary the antecedent conditions at will by successively utilizing new and different samples—samples in which additional variables may be controlled as such variables become apparent at successive stages in the research.

For purposes of immediate prediction and control the cross-sectional method seems to be the appropriate one. Even if there were ways of assessing the effect of attrition upon a longitudinal sample, the fact remains that none of the major longitudinal studies (2, 5) have yet covered an adequate enough portion of the adult age span on which to base generalizations regarding the aging process. There is immediate need for data concerning intellectual and personality changes in an adult population for whom few or no genetic records are available. It is the purpose of this paper therefore to re-examine some of the pitfalls of the cross-sectional approach and to propose certain useful methods in coping with them. Some of the findings of a major cross-sectional study (7) will be used for illustration.

PROBLEMS AND PROCEDURES

Among the most serious criticisms of the cross-sectional method for studying the effects of age has been the contention that it is extremely difficult to secure comparable samples of the population at different age levels. Some writers (4, 5) have argued that one might mistake cultural changes for effects of aging. This sampling problem has been discussed by Dennis (3), Shock (8), and Strother, Schaie, and Horst (9).

One concern is with differences in educational background within the sample. It is held that, due to increased educational opportunities, the younger groups will have an advantage in most pencil and paper tests over the older groups. The younger groups also may have an advantage in novel test situations because their better education has given them experience in a wider range of situations.

A second concern is with the effect of differing ranges of talent. Some investigators, while successful in obtaining reasonably broad samples of younger groups, rely on rather restricted sources for their middle-aged and older subjects. Other investigators report that, due to the strange and emotionally threatening aspects of psychological testing, their older volunteer subjects tend to represent more restricted ranges of talent and personality characteristics than do their younger. Most evidence which might bear on this restriction of range, however, is reported in anecdotal or grossly descriptive form without attempt at formal evaluation of the extent to which this factor does or does not invalidate the principal findings of a given study.

While some of these criticisms are specific to studies of aging, the problem of drawing valid group comparisons when differential selection factors may be operating is a problem in most studies using volunteer subjects. The generalizations made from any study are necessarily limited by the extent to which the sample replicates the composition of the general population. When volunteer subjects are used, such replication is often in doubt. Although census type sampling procedures might be more appropriate than volunteer types, they are expensive and lie beyond the scope of the average investigator. A reasonable and frequent compromise consists of an experimental design requiring a given quota of subjects stratified with respect to one or more crucial characteristics. A random sampling procedure is then used within each of

the major stratifications to provide adequate sampling with respect to other uncontrolled variables.

Such a design is characteristic of cross-sectional studies of age changes (2, 6). Stratification is in terms of age, and random selection is attempted with respect to other variables. The assumption is then made that any change on the measurement variable may be attributed to a function of "aging." Whether this assumption is at all tenable depends largely on how successful the random selections within the age strata have been in yielding comparable groups. The likelihood of such success is often, in turn, a function of the size and nature of the parent universe from which prospective subjects have been drawn.

A critical examination of the particular sampling procedure employed is therefore in order in evaluating any cross-sectional study. It is necessary to define precisely the nature of the sampling universe from which subjects are drawn, to describe the relation of this universe to the general population, and to describe how accurately this universe is replicated by the final sample of subjects.

If there is reasonable satisfaction at this step one may then return to the problems presented by the lack of comparability of the population attributes among the various age levels within the sample. First of all it is necessary here to specify the relevant attributes which could introduce confounding artifacts. Next, information regarding these attributes must be gathered for each subject. A formal analysis must be conducted to test the hypothesis that there are indeed sub-group differences on these relevant attributes. If significant differences are found it becomes necessary to re-evaluate the findings with respect to age change. Analysis of covariance would usually be the most appropriate procedure for such re-evaluation.

To obtain maximally valid results from a cross-sectional study of aging, then, the procedures may be summarized as follows:

1. The sampling universe from which subjects are to be recruited must be clearly defined:
   a. some of its population attributes should be known;
   b. it should be large enough to permit random sampling;
   c. motivation should be relatively equal for most of its members;
   d. it should be representative of a larger population (if generalization is important).
2. Population attributes which may confound the effects of aging must be specified. (These attributes will generally include socio-economic variables such as education, income, and occupation).
3. Information on these attributes is collected on all experimental subjects.
4. The hypothesis that there are differences in these attributes between age groups is tested.
5. The analysis of covariance is used to test the effect of any significant factors (found in step 4) in re-evaluating the main findings of the study.

AN EXAMPLE

An application of these procedures is to be seen in a recent study of the relationship between rigidity-flexibility and intelligence over the age span 20 to 70 (7). This was a cross-sectional study of volunteer subjects in which the stratified-random sampling technique was used. The universe was stratified by age (and by sex, by assigning an equal number of men and women to each stratum) and random selection was made within each stratum with respect to other variables. One of the findings in this study was the significant decline of intellectual functioning with age as measured by Thurstone's Primary Mental Abilities Test (10). The present paper will test the hypothesis that this finding was an artifact of the cross-sectional method.

Sampling Procedure

The methods used to obtain subjects for the study to be described are believed to be a good example of how data on human subjects may be obtained effectively and inexpensively by community-oriented cooperative research methods. The methods also provided for maximum motivation of participants without resorting to motivating devices which are artificial or in bad taste.

It was possible to obtain the cooperation of the Group Health Cooperative of Puget Sound (Seattle), a non-profit pre-paid medical plan based on group practice and covering about 40,000 individuals. The administrators were interested in obtaining data on the attitudes of members toward the services provided, but they lacked funds and facilities to engage in a survey of their own. A cooperative research project was agreed upon for which the Group Health Cooperative placed their membership lists at the disposal of the investigator and provided the motivating appeal for volunteer participation. The investigator in return collected, in addition

to his own data, the survey data desired by the medical administrators.

The appeal to the sample of prospective volunteers was made in terms of their interest in improving the medical services made available to them. While no information was given about the tests to be administered, it was indicated that a variety of personal information was to be collected for research purposes. (It is felt that this approach secured a wider range of subjects within the final sample than would have been obtained had the prospective subjects been solicited for the specific purpose of taking psychological tests. This method would also appear acceptable from a public relations point of view, since no more than one or two hostile responses were encountered during recruitment.)

It has often been observed that the likelihood of obtaining volunteers may be a function of the difficulty involved in their participating. To obtain a good cross-section of urban and suburban populations, testing locations were established in widely dispersed but easily accessible public school facilities throughout King County (the geographic limits of the group health plan). Prospective volunteers selected locations and times convenient to them, and returned this information on a prepaid postal card included in the contact letter. (This procedure was expected to minimize the effect of area of residence in biasing the sample.)

All potential subjects returning favorable replies were then contacted by telephone, and specific appointments for group testing sessions were made. Subjects were contacted in the order in which their replies were received until the desired quota for each age stratum was slightly over-subscribed. More subjects were actually tested than were required by the experimental design. (This allowed amply for the incidental "spoilage" which is inevitable in group testing situations.)

Drawing a stratified sample. The original design of the study called for 12 groups of 50 subjects (half men and half women), one group at each five-year age interval from 16 to 75. The ratio of potential to actually participating volunteers was assumed provisionally to be 1 to 5; i.e., it was felt that for each subject to be tested, five would have to be contacted. Therefore, the names of 250 potential subjects at each age interval, or a total of 3,000 names, were to be obtained.

The Group Health Cooperative consisted of about 40,000 persons. This number was reduced to a pool of approximately 18,000 potential subjects by eliminating children under 16 years of age and all persons who were covered by group contracts and whose individual addresses were not available. While the total membership of the Group Health Cooperative was found to be quite representative on socio-economic indices of the urban and suburban population of the State of Washington (as compared to the 1950 census data), the deletion of group-contract members led to a depletion of potential subjects at lower social class levels. The remaining pool of subjects is therefore primarily drawn from the middle classes, including the upper levels of the working class, but does not draw appreciably from the lower working class or the upper class of American society.

Individual IBM cards giving name, sex, and age for each subject were available, and these cards were sorted by year of birth and sex. Cards for 25 men and 25 women for each year of birth from 1880 to 1939 were then withdrawn by re-sorting and removing every card in the "0" pocket of the card-sorter until the necessary number was reached, starting alternately at the beginning and at the end of the alphabet.[1] After those persons who no longer lived within the King County area had been eliminated, a sample of 2,818 potential subjects remained.

In response to the request for participation sent to the 2,818 persons, positive replies were received from 451 men and 459 women. (This represents a positive response of 32.3 per cent.) Table 1 shows the age and sex distribution of the sample of contacts and the frequencies of positive responses. Marked age as well as sex differences in the frequencies of volunteer participation were found, with peak participation for both men and women occurring in the age group 36 to 40. (The implications for cross-sectional studies are obvious—to obtain specified samples of volunteers, the investigator should use different sampling ratios at different age periods.

[1]During this operation it was found that there were not enough potential subjects in the 71 to 75 year bracket available to fill the desired quota. All available names were retained, but when it became evident later that there was no satisfactory sample for this age group it was dropped from the design. It was also subsequently found that volunteer response in the 16 to 20 year old group was insufficient, and this group was also dropped. The description of the final sample will therefore cover the range 20 to 70 years of age. Analyses of the relationship of the population of contacts to the sampling universe, however, will include data on all twelve groups from 16 to 75 years of age.

From the pool of 910 volunteers it was possible to make testing appointments for about 600 people. The attrition may be explained by conflicting schedules, participants failing to keep appointments, and other miscellaneous problems. After removing faulty or incomplete test records and after dropping the individuals from the youngest and oldest age groups, complete records were available on a sample of 500 individuals ranging in age from 20 to 70 years. These were divided into 10 five-year intervals, each containing 25 men and 25 women. The final sample closely replicated the population of contacts, suggesting that the sampling design and methods of obtaining subjects were satisfactory in obtaining the stratified sample desirable for a cross-sectional study. It would also appear that the use of the 1 to 5 ratio of potential volunteers to obtained subjects was reasonable and realistic.

Attributes of the Sample

The attributes which are generally considered likely to produce artifacts in studies of aging are mostly socio-economic. For the present study they included: education, income, occupation, marital status, family size, and mobility (as assessed by measures of residential stability, job mobility, and occupational mobility). This information was collected at the same time as the experimental data. The most relevant measures appear to be the ones on occupation, total family income, and years of education completed. Table 2 gives the mean and standard deviation for each age group on these variables.

Education. Of the total sample, 11 per cent had no more than a grade school education, 42.4 per cent had attended or completed high school, 32.6 per cent had attended or graduated from college, and 14 per cent had done some post-graduate work in addition to their college education. The mean number of years of education was 12.7 for the male and 13.0 for the female subjects. In terms of age differences, mean number of years of schooling varied from 11.0 years for the 61- to 65-year-old group to 14.1 years for the 25- to 30-year-old group. These differences are significant and, since they compare closely with those reported in the general census data, seem to reflect the increased educational opportunities available for all younger people rather than differences in the population from which the subjects were obtained.

Occupational level. All subjects were rated as to occupational level on a scale ranging from 0 (unskilled laborer) to 9 (professional), using the major classifications employed by the U. S. Bureau of the Census. Where the occupation "housewife" was given, the occupational rating of the husband was used. College students were arbitrarily rated 7 (managerial and proprietors) and graduate students were assigned to level 8 (semi-professional).

According to this classification, the sample contains 1.2 per cent unskilled laborers, 0.8 per cent employed in domestic service, 3.6 per cent

TABLE 1. AGE AND SEX DISTRIBUTION OF THE TOTAL POTENTIAL SAMPLE; AND FREQUENCY OF POTENTIAL SUBJECTS WHO VOLUNTEERED.

Age Group	No. of Contacts			No. of Contacts who Volunteered			Per Cent of Contacts who Volunteered		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
16 - 20	116	124	240	19	33	52	16.4	26.6	21.7
21 - 25	117	123	240	23	36	59	19.6	29.3	24.7
26 - 30	121	116	237	35	43	78	28.9	37.1	33.0
31 - 35	122	122	244	46	41	87	37.6	33.6	36.0
36 - 40	123	120	243	54	46	100	43.8	38.3	41.0
41 - 45	129	126	255	42	45	87	32.6	35.7	34.2
46 - 50	123	117	240	49	41	90	39.8	35.0	37.5
51 - 55	126	116	242	47	36	83	37.3	31.0	34.3
56 - 60	118	116	234	33	38	71	27.9	32.8	30.4
61 - 65	119	113	232	39	40	79	32.7	35.4	34.0
66 - 70	145	132	277	39	43	82	26.9	32.6	29.7
71 - 75	69	65	134	25	17	42	36.3	26.2	31.3
Total	1428	1390	2818	451	459	910	31.6	33.0	32.3

operatives, 5 per cent in the service occupations, 5.8 per cent in the protective services, 13.6 per cent skilled craftsmen, 31 per cent in sales or clerical work, 16.3 per cent at the managerial or proprietory level, 15.2 per cent engaged in semi-professional, and 5.2 per cent in professional occupations.

The mean occupational level for different age groups varies only slightly, from 5.2 to 6.4. The age differences show a systematic trend, with age groups over 50 having the lower average levels. (This may indicate a tendency for older people to gravitate towards lower-level jobs whenever job change is inevitable.)

Income level. All subjects were asked to indicate their total family income by checking a six-step scale divided into intervals of $2,000 and ranging from "below $2,000" to "above $10,000." On this scale, 6.6 per cent of the sample indicated total family income "below $2,000." The proportions at successive income levels were: 18.8 per cent, 41.8, 18.2, 10.4, and, at the "above $10,000," 4.2. As expected, age differences were found in income level, with mean income dropping off after age 50 and decreasing steadily thereafter. The mean income level for the entire group was found to be 3.2, which would be equivalent to a total annual family income of about $4,500.

Marital status and family size. Since the parent pool of subjects were primarily members of a family medical plan, most of the subjects (except for the youngest age group) were married. There is a sprinkling of single, widowed, and divorced persons throughout. Of the total sample, 6.6 per cent are single, 83 per cent are married, 2.6 per cent divorced, and 5.8 per cent have been widowed. The distributions by marital status were approximately the same for the age groups except for the youngest group, where there is a high incidence of single people, and the oldest groups, where evidence is found of family dissolution through the death of one of the partners.

Data on family size show a wide range from no children to 10 children, and also show some age variation which seems to reflect the economic climate at the time when members of each specific age group were at their maximum fecundity period. The average subject has two children, with 21.8 per cent of the group having no children, 44.6 per cent having one or two children, 29 per cent having three or four children, and 4.6 per cent having five or more children.

Measures of mobility. It is often important to know whether the sample replicates the stable portion of the community, particularly if one is concerned with follow-up studies at a later time. To yield some information on this problem three measures were selected: 1) frequency of change in living quarters during the past five years; 2) number of job changes during the past five years; and 3) number of different types of jobs or professions held during the past five years.

On frequency of residential change rather marked mobility is shown for the younger age groups with increasingly lessened mobility for the older subjects. The subjects changed their residence on the average once during the past five years. But 56 per cent of the population made no change at all, 21.4 per cent moved once, 7.8 per cent twice, 7 per cent three times, 4.2 per cent four times, and 7.8 per cent moved five times or more during this period.

The next measure of mobility is the frequency of employment changes. The mean number of employment changes turns out to be 0.6 for the group as a whole. Seventy per cent of the group apparently retained the same job they held five years ago, 14 per cent changed once, 6.2 per cent twice, and 9.8 per cent three times or more. Consistent age differences are shown to exist, with job mobility decreasing until about the fifth decade, at which time a plateau seems to be reached.

The final measure of mobility was the number of different job classifications or professional specialities the subject held during the past five years. The average member of the group has held 1.2 different occupations during the past

TABLE 2. SOCIOECONOMIC CHARACTERISTICS OF THE SAMPLE (N = 500).

Age	Years of Education		Occupational Level		Income Level	
	$\bar{X}$	Σ	$\bar{X}$	Σ	$\bar{X}$	Σ
20-25	13.0	2.26	6.3	1.38	2.7	1.11
26-30	14.1	2.40	6.4	1.33	3.3	0.79
31-35	13.9	2.60	6.1	1.70	3.6	1.04
36-40	13.5	3.00	6.2	1.68	3.9	1.13
41-45	13.5	2.60	6.1	1.82	3.6	1.06
46-50	13.7	2.95	6.4	1.73	3.9	0.99
51-55	12.6	3.55	5.8	2.08	3.4	1.13
56-60	12.1	2.92	5.7	1.69	2.7	1.03
61-65	11.0	3.71	5.5	1.89	2.6	1.04
66-70	11.1	3.18	5.2	2.15	2.2	1.09

five years. Of the total sample, 84.6 per cent have continued in the same occupation or profession, 11.2 per cent have made one change, and 4.2 per cent have made two or more occupation changes. As with the frequency of job changes, occupational mobility appears to be characteristic only for the early portion of adulthood, almost no mobility being present after the fourth decade.

TEST OF THE PRINCIPAL HYPOTHESIS

At this point the question may be asked whether the information about sample characteristics has any bearing on the validity of the observed age changes on the Primary Mental Abilities Test. Table 3 summarizes the results of the analysis of variance testing the significance of the differences between age groups on the PMA subtests. In every instance the null hypothesis has to be rejected at or beyond the 1 per cent level of confidence. These are the findings which are now to be evaluated.

An analysis of the data in the previous section of this paper leads to the conclusion that there are indeed significant differences between age levels on the socio-economic attributes of education, income, and occupation. The measures of marital status and family size, however, do not seem to vary in direct relation with age. Measures of mobility are age-related, but age gradients on these measures reach a plateau in the forties (at the point where changes in intellectual functioning are generally shown to become significant). It is apparent, therefore, that the first three variables are the proper ones to be used for a test of the hypothesis that findings regarding age changes in intellectual functioning are artifacts of the sampling procedure.

TABLE 3. RESULTS OF THE ANALYSIS OF VARIANCE TESTING THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN AGE GROUPS ON THE PRIMARY MENTAL ABILITIES TEST.

Variable	Between-group variance	Within-group variance	*F* ratio[a]
Verbal-meaning	1,202.55	79.91	15.05
Space	1,220.22	91.11	13.69
Reasoning	1,603.27	72.61	22.08
Number	448.70	93.05	4.78
Word-fluency	517.37	92.61	5.59
Composite IQ	1,215.81	79.57	15.28

[a] With 9 and 490 degrees of freedom respectively, an *F* ratio will be significant at the 1 per cent level of confidence if it exceeds 2.45.

As a first step, use was made of a procedure described in a paper by Strother, Schaie, and Horst (9) which shall be referred to as the "Method of Multiple Mean Adjustment."[2] The purpose was to correct group means on any given variable for the effect of one or more other factors without the necessity of correcting each individual score. The computations involved require the calculation of the beta regression vector of each of the variables to be corrected upon the correction factors. Table 4 gives the necessary beta weights and the multiple correlations. Table 5 lists the mean PMA T-scores before and after correction, as well as the differences between these scores. In order to be significant, a difference would have to attain a magnitude of 4.0 score points at the 5 per cent and 5.3 score points at the 1 per cent level of confidence. None of the differences between the raw and adjusted means are therefore significant.

The analysis of covariance was next used for a formal over-all test of the hypothesis that the experimental results are due to sampling artifacts. In addition to the multiple regression of the three socio-economic measures upon the Primary Mental Abilities scores for the total sample (shown in Table 4), comparable data were now needed also for the within age level component of variance. The appropriate within-group beta weights and multiple correlations are shown in Table 6. The data from Tables 4 and 6 were now used to adjust variances in the PMA data (Table 3). The result of these analyses of covariance adjustments is presented in Table 7. If the null hypothesis is true then these adjustments should reduce the effect of age differences to the point where they become insignificant. In spite of the adjustments, however, the differences remained significant. The null hypothesis is thus rejected. It must be concluded that the significant sub-sample differences on three socio-economic variables do not affect the validity of the findings with respect to age changes on the Primary Mental Abilities Test.

SUMMARY AND CONCLUSIONS

The principal purpose of this paper was to evaluate the criticism that the results of cross-

[2] A complete description, mathematical derivation of the correction formula, and computational instructions for the "Method of Multiple Mean Adjustment" may be found in Strother, C. R., Schaie, K. W., & Horst, P., The relationship between advanced age and mental abilities. Unpublished manuscript, Document No. 5299, American Documentation Institute, 1955.

sectional studies of psychological effects of aging are suspect because of the non-comparable nature of samples at various age levels. Appropriate aspects of cross-sectional methods were discussed, and a representative study was closely examined to provide evidence for or against the criticism.

One of the principal findings of the study used for this analysis was that there were significant age changes on the Primary Mental Abilities Test. The present paper raised the hypothesis that such findings could be an artifact of the cross-sectional sampling procedure. The Method of Multiple Mean Adjustment and analysis of covariance were used to test this hypothesis by adjusting for the effect of the significant socio-economic variables. These adjustments did not have any appreciable effect upon the main experimental findings being examined.

The results of the present paper would suggest that sampling over the major portion of the adult age range does indeed lead to the selection of sub-samples which show significant differences in their socio-economic composition. These sub-sample differences, at least in the example reviewed, do not necessarily affect the results on the psychological age

TABLE 4. BETA REGRESSION WEIGHTS AND MULTIPLE CORRELATIONS (TOTAL SAMPLE).

	Verbal-meaning	Space	Reasoning	Number	Word-fluency	Composite IQ
Years of education	-.192	-.236	-.247	-.080	-.079	.084
Income level	.360	.214	.355	.171	.104	.043
Occupational level	.499	.302	.478	.350	.422	.367
R^2	.3336	.0750	.2679	.1489	.1712	.2073
R	.578	.274	.518	.386	.414	.455

TABLE 5. AGE CHANGES ON THE PRIMARY MENTAL ABILITIES TEST. MEAN SCORES BEFORE AND AFTER CORRECTION BY THE METHOD OF MULTIPLE MEAN ADJUSTMENT.

Age level	Verbal-meaning			Space			Reasoning			Number			Word-fluency			IQ Composite		
	$\bar{X}$	$\bar{X}c$	$\bar{X}c-\bar{X}$	$\bar{X}$	$\bar{X}c$	$\bar{X}c-\bar{X}$	$\bar{X}$	$\bar{X}c$	$\bar{X}c-\bar{X}$	$\bar{X}$	$\bar{X}c$	$\bar{X}c-\bar{X}$	$\bar{X}$	$\bar{X}c$	$\bar{X}c-\bar{X}$	$\bar{X}$	$\bar{X}c$	$\bar{X}c-\bar{X}$
20 - 25	51.4	52.4	1.0	54.8	55.4	0.6	56.2	57.9	1.7	47.5	47.4	-0.1	50.0	49.8	-0.2	51.9	51.8	-0.1
26 - 30	55.4	55.1	-0.7	55.9	55.9	0.0	55.9	55.7	-0.2	50.6	49.7	-0.9	51.1	50.2	-0.9	54.2	53.4	-0.8
31 - 35	55.5	55.1	-0.4	55.3	55.1	-0.2	55.4	55.5	1.1	52.4	51.8	-0.6	53.7	53.4	-0.3	55.4	55.2	-0.2
36 - 40	52.8	50.4	-2.4	53.0	51.9	-1.1	52.4	50.1	-2.3	51.3	49.9	-1.4	50.6	49.5	-1.1	52.4	51.7	-0.7
41 - 45	52.6	51.4	-1.2	51.0	50.4	-0.6	53.0	52.0	-1.0	52.3	51.7	-0.7	52.8	52.4	-0.4	53.1	52.8	-0.3
46 - 50	52.3	49.0	-3.3	50.0	48.6	-1.4	50.3	47.0	-3.3	53.3	51.7	-1.6	52.4	50.9	-1.5	52.4	51.1	-1.3
51 - 55	49.1	47.7	-1.4	47.8	47.1	-0.7	48.4	47.0	-1.4	52.1	51.8	-0.3	51.2	51.0	-0.2	50.1	50.1	0.0
56 - 60	46.6	47.9	1.3	45.2	45.8	3.6	45.4	46.3	0.9	50.1	51.2	1.1	49.2	50.0	0.8	47.0	47.9	0.9
61 - 65	43.0	43.6	0.6	45.4	45.7	0.3	42.0	42.3	0.3	45.1	46.0	0.9	45.2	46.0	0.8	42.6	43.6	1.0
66 - 70	41.3	43.8	2.5	41.6	42.9	1.3	40.9	43.1	2.2	45.3	47.3	2.0	43.7	45.2	1.5	40.9	42.3	1.4

TABLE 6. BETA REGRESSION WEIGHTS AND MULTIPLE CORRELATION (WITHIN GROUPS).

	Verbal-meaning	Space	Reasoning	Number	Word-fluency	Composite IQ
Years of education	.292	.103	.279	.175	.083	.320
Income level	.107	.022	.179	.035	-.054	-.065
Occupational level	.242	.060	.150	.205	.382	.242
R^2	.2983	.0262	.2454	.1360	.1840	.2598
R	.546	.162	.495	.367	.429	.510

TABLE 7. RESULTS OF THE ANALYSIS OF COVARIANCE TESTING THE EFFECT OF THE REGRESSION OF THE PRIMARY MENTAL ABILITIES UPON THE MEASURES OF EDUCATION, INCOME, AND OCCUPATIONAL LEVEL.

Variable	Adjusted between-group variance	Adjusted within-group variance	F ratio[a]
Verbal-meaning	647.89	56.42	11.48
Space	886.67	89.27	9.93
Reasoning	1,084.78	55.13	19.68
Number	315.89	81.67	3.87
Word-fluency	493.33	76.03	6.49
Composite IQ	1,191.11	59.26	20.10

[a] With 9 and 487 degrees of freedom respectively, an F ratio will be significant at the 1 per cent level of confidence if it exceeds 2.44.

changes studied. Any cross-sectional study of aging, however, should be designed in such a way that the effect of differences in the population attributes of sub-samples can be assessed and controlled by statistical techniques. Appropriate techniques for handling this problem have been indicated.

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MAJOR PROBLEMS OF INDUSTRIAL GERONTOLOGY*

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Most work in the field of social gerontology is directed toward solving the problems of the elderly, retired individual who by the very nature of his increasing difficulties in living makes impelling demands upon the social conscience of his fellow citizens. Yet the period after retirement is comparatively short. Wolfbein (16) has shown that for American men about 42 years are likely to be spent in work compared with eight years in retirement. There are only a few studies dealing with the problems which face men in the latter half of their working lives. There is even less on the organizational problems of industry in coping with older workers. As it is, the young are well looked after, trained, and given opportunities for advancement; the old are being increasingly cared for; but those who are neither young nor old are left to get on with their developing problems as best they may.

The study of the problems of the older worker may be called industrial gerontology, and its importance lies not only in the contribution which it may make to the well-being of the older workers themselves, but also in the contribution it could make to higher productivity through establishing conditions under which older men can make optimum use of their skills. Industrial gerontology will be concerned with older workers at all levels in an industrial organization, both those employed on administration and those on the shop floor. It would seem, however, that the problems of the non-manual worker, although of equal importance to those of the manual worker, are of a somewhat different nature, and they will not be considered in this paper.

The following two cases illustrate some of the problems of the manual worker which need to be investigated.

A. R. was born in Birmingham (England) in 1892. He left school at the age of 14 to work as a shop boy in a firm manufacturing light castings. In this capacity he was able in time to learn some machining and he also attended night school regularly. At 19 he was graded as a semi-skilled machinist.

He served in World War I, rising to the rank of sergeant; and upon demobilization he returned to his previous job. In 1920 he was made a charge-hand; but in 1924 he was discharged due to a reorganization of the firm. He was out of work for 9 months, then was employed as machinist in a light general engineering firm.

He was discharged in 1930 and was unemployed, except for a short period as a garage hand, until in 1933 he secured employment in a motor car plant. Here he worked on an assembly line at a lower rate of pay than he had received on earlier jobs. He held this job without change until 1939 when he found it difficult to maintain the pace of the line. He found another job as a cutter-off in a tube works.

In 1941 he dropped a tube and damaged the toes of his right foot. This left him with a limp and at times he had pain when standing. In 1944 when reaching to the back of his machine to lift a tube into position he strained his back. He said nothing at the time, but he found it increasingly difficult to continue his work without pain. He saw the medical officer who recommended that he should take a lighter job. He tried to get transferred to inspection where he might spend less time standing, but the firm felt he was too old for an inspector's job and offered him instead a job as a packer. He felt himself unable to accept the down-grading involved and so was discharged at the age of 55. At this age he had difficulty in finding another job in engineering and, being a Registered Disabled Person, took a job as an elevator operator.

He would like to retire at 65, but he is continuing to work because he has no pension other than the Old Age Pension, and because his savings were exhausted during his periods of unemployment. Although his injured foot and back make standing painful, he is mentally alert; and he is still able to exercise some of his skill and to supplement his income by making toys in his workshop at home.

J. C. was born in 1897 and at 14 was apprenticed to a motor firm. On completing his apprenticeship he became a skilled machinist working mainly on milling. He served in World War I but did not return to his old job because the firm had been merged with another.

He took a job as a borer; after two years became a charge-hand; and in 1926 moved, as foreman, to a small specialist firm of die makers. In 1931 the firm went into liquidation. He was able to regain employment as a miller in a large general engineering firm, but with loss of seniority. Seeing no prospect of promotion he moved again in 1937 to the South West of England into the aircraft industry. He was, however, unsuccessful in gaining promotion and remained on the machine first as a grinder, then as a miller, and finally, throughout the war, as a turner.

Soon after the war he began to experience low back pain when bending over his lathe. He also had in-

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creasing difficulty with his vision, possibly due to long periods of working to fine tolerances in poor light. As a result, when the firm brought in consultants to establish a bonus system, he found it difficult to make the bonus. He tried to get promoted to a supervisory position but was turned down because of his age (50 years) and was turned down also for an inspection job because of his poor vision.

In 1950, having saved a little money, he resigned and bought a small tobacco and newsagent business. In 1954 his wife died. He sold the business, and eventually found a job washing motor coaches and doing minor repairs.

These two case studies illustrate a number of problems of industrial gerontology. Both men made major changes in their jobs; both suffered disability through poor work design; both ended up, through no fault of their own, in jobs which were below the highest status each had achieved; one was unable to survive the introduction of a bonus scheme; both were unable to secure other jobs with their present employers when they were unable, through disability, to continue in their original jobs; one was unwilling to take a job involving loss of status; one was refused promotion because of his age; both suffered setbacks in their careers during the depression of the early 1930's, when one was 35 and the other 40—setbacks from which neither was able to recover; neither made any attempt nor was afforded the opportunity to move into other work where he would have to learn a new skill; one left an assembly line because he found it difficult to maintain the pace.

For convenience we will discuss these problems separately, but in fact many of them may react one with the other, sometimes as causes and sometimes as effects.

CHANGES IN JOBS

Quite apart from changes in employer when men remain in the kind of work for which they were originally trained, they may during their working life be faced with the need to move to work which is unfamiliar. These changes may be minor or major. A minor change is of the kind made by *A. R.* when he moved to tube cutting—the job was new to him but had points of similarity to jobs he had held previously. In common with some major changes, a minor change may involve a measure of retraining, a point which will be discussed below. A major change would involve the decision to move to something quite new and unfamiliar. In effect this may be a "first retirement," and it may raise as many or more problems for the individual as does final retirement at age 65 or older.

J. C., it will be remembered, with his failing sight, had to make up his mind whether to carry on or to risk his savings in a new venture. He was faced with a similar difficult decision when he lost the help of his wife through death: would he struggle on alone or make yet another major change, another retirement? While he may expect to get help with his problems after he has finally retired and when he is old and lonely, he will have had to face his earlier retirement alone. To industry he was a clock number which was not paying its way. The social gerontologist, on the other hand, preoccupied with the problems of old age, seems to be able to offer little help.

It is obvious that a great deal more needs to be known about the problems men face when they need to make a major change in their work patterns. It should become customary to speak of withdrawal from the working force as a final retirement, thus recognizing that for many men there may be, in addition, a first, second, or even a third retirement.

LOST SKILLS

Both our subjects left the engineering industry when they might still have served at least another ten years. That loss of skilled men may occur during middle age is suggested by a survey of the engineering industry which showed that most of the more highly skilled jobs were held by men whose ages were from three to 13 years below that of the industry as a whole (10, 11). In one large firm this inverse relationship between age and level of skill employed has remained roughly static over eight years.

The causes of this inverse relationship are not altogether clear. Nor is it known what happens to men who must move from the more highly skilled jobs. Do they stay in the same industry, but take jobs which are below the best of which they are capable? Or do they leave the industry altogether?

It was also shown in the study referred to above (11) that men are unlikely to stay in the same firm on a job which is inferior in status to their earlier job—practically all internal transfers over eight years in one firm were to superior jobs. Evidence is also given by Belbin (1) that men were rarely transferred to lower paid work before the age of 60 except on medical grounds.

WORK DESIGN

Until recently most machines have been designed without much consideration for the long-term effects on their operators. This is not entirely the fault of the designers, since so few studies have been made of the long-term effects to be expected from various features of design. It is only recently that data that will enable equipment to be produced as a man-machine entity have been made available to designers in usable form (8, 9, 17). As far as aging is concerned, pilot job analyses by Griew and Tucker (5) have suggested some modifications which might be made involving such factors as posture, complexity of control, or the extent of physical activity required.

Yet any observant person who visits an industrial plant can hardly fail to see many instances of unsatisfactory work design. These may include such features as bad posture, bad seating or absence of seating, limbs used in unnatural positions or beyond their normal limits, poor lighting, radiant heat stress, poor scale design (particularly on measuring instruments), too great a complexity of control functions, unsatisfactory instructions, overloading of one sense modality, and unsatisfactory cues for action. These hazards are far less dramatic than, for instance, chemical poisoning or conditions causing pneumoconiosis, and so may often be unrecognized. Thus, while it is difficult to believe that a man who for twenty years has to bend over a lathe, or stand on one leg at a press, or work with one arm raised above his head can fail to suffer some ill effects, there are at present insufficient data relating disability to working conditions. It is possible that some of the ill health suffered by the elderly could be traced back to bad machine design.

In addition to long-term effects, poor work design may also make it increasingly difficult for an older man to continue doing certain jobs, and so may be a major determinant of the relationships between age, level of skill employed, and loss of skilled men to the industry. This view is supported by a finding of Griew (4) that older men employed on "young" jobs have more accidents than would be expected.

One aspect of work design on which there is some information is the pacing of work by machines. A machine which forces the operator to work at a constant rate will subject him to stress (3). This type of stress seems to be too great for men over 50 years of age (1, 2); perhaps because the older men become slower or because they have greater variability in their cycle times. In either case they will miss more "beats" or find the strain of keeping up with the machine too much for them.

BONUS SCHEMES

A feature of the last 25 years has been the widespread introduction (at least, in the United Kingdom) of bonus systems of payment. These schemes have often been introduced piecemeal without, it seems, any regard for the human problems involved. While the effect of some of these schemes has been reduced by the fallibility of rate fixers, by bargaining over rates, and by restriction of output to a target, there is no doubt that bonus systems, in some instances, work to the disadvantage of the older man. It seems probable that where rates are "tight," and pressure is brought to bear on young and old alike to achieve a high production, the inevitable slowing of the older man is bound, in the end, to take its toll. If the standard set is that of the best workers, and those falling below (and these must be the majority) are, as it were, considered to be failing in their jobs, then the older men must suffer more than if the standard is set lower and those who surpass it are considered superior.

An unpublished study by Murrell, Griew, and Young at Bristol (12) has suggested that on the whole older men prefer a group bonus and dislike individual bonuses, often on the grounds that quality suffers (a study of the attitudes of older and younger men regarding quality of output might be revealing). On the other hand, some younger men dislike group bonuses on the ground that older men with whom they may have to work are slower and pull the bonus down for everyone—a point that usually is not admitted by the older men.

Since it seems that, for better or worse, these bonus schemes are likely to be a feature of industry for some time to come, their effect on the older worker should be investigated.

PROMOTION

The term "promotion" is usually used to imply elevation from the shop floor to supervisory grades: charge-hand, setter, or foreman. In this sense, it is subject to company policy which, as with hiring policy, is founded on experience or custom. In another less commonly used context it can mean upgrading or movement to a

job that carries higher status, even if that job carries no greater authority or financial advantage.

In formal promotion there appears to be a discrimination against older men similar to that which is found in hiring. In the firm investigated by Murrell, Griew, and Tucker, of some 775 men who were aged 49 or over 1947, not one had been promoted eight years later. Interviews with men in another firm showed that most of the men over 50 had given up hope of any further promotion, and had resigned themselves to "soldiering-on" until they were pensioned.

It must be recognized that perhaps only one in ten can end up as foreman, and it might be supposed that by the age of 50 all the promotable individuals in a cohort will have been promoted. The latter is not necessarily so, however, for luck can play too large a part—as it did with *A. R.* and *J. C.*, both of whom became supervisors but then lost these posts through no fault of their own. To the outside observer it would seem that the loss of hope of further promotion (such as that experienced by officers in the Royal Navy who have been "passed over") must result in loss of incentive to the man over 50. Little or nothing is really known about the ability of older men to make good in supervisory grades; about the effect on work attitudes of being passed over; or about the effect of seeing younger men, whom they themselves may have trained, being put in authority over them.

Quite apart from promotion to supervisor there is movement to jobs which may carry a higher status in the informal hierarchy of an industrial community. Welford tells the story of a Cambridge College porter who was moved from the Front Lodge to the Back Gate. He pleaded to be allowed to return to his former post; his wife was being ostracized by the neighbors because of his believed loss of status. Status may be a powerful driving force (even the rat catcher now prefers to be called a rodent exterminator); and job movements which seem quite reasonable to management may well cause discontent because to the shop floor worker they involve a loss of status. As was mentioned earlier, in their study of job changes in a firm over a period of eight years, Murrell, Griew, and Tucker (11) found that practically all moves were made to jobs which appeared to be "superior." They suggested that older men would leave a firm rather than admit that they could no longer cope with a job and rather than accept a job which involved loss of status. Belbin (1) also reported that in his industrial studies he found no evidence of downgrading of men under the age of 60. It would appear that any downgrading which does take place must occur when a man moves from one employer to another.

The relative status of jobs in a company may be the result of tradition over the years (recent troubles in the shipbuilding industry in the United Kingdom seem to have arisen from the fears of a "craft" union that their members were losing their status). Yet employers may be able to create "status" jobs which need not necessarily involve either higher payment or responsibility, and which can be used to raise the morale of the older man who finds his accustomed work becoming too difficult.

TRAINING

It is generally believed that it is of little use to give most men over 40 training in a new job. Shooter and King (14) have examined a number of training schemes and have found that the performance in these courses of men over 40 was progressively inferior to that of younger trainees. They point out, however, that this finding is based on averages and that it is due not so much to a general lowering of the level of achievement but to greater individual differences. They suggested further that the criteria by which success is judged (which frequently involve time stress) tend to favor younger trainees, and that success or failure is judged on performance at the end of the course and not on subsequent performance on the job.

At first sight this may appear to confirm common belief; but in fact the number of men over 40 being trained is so small, and the data on their trainability are so scanty, that the best that can be said is that the current methods for training men over 40, where they exist, have not been very successful. This leaves wide open the question whether, if other methods had been used or other jobs chosen, greater success would have resulted.

The view is also held that late starters in jobs such as drafting will not be able to advance beyond the lower grades, and that to train older men for such jobs would be unfair to them. But the financial difficulties of an older man may be greater and his status lower if he is thrown on

the labor market without any retraining than would be the case if he were retrained for a job of lower status than the one he once held.

At present it appears to be more economic for firms to train younger men who, on the face of it, seem likely to give longer service in return, than to train older men. In addition, older men often have greater family responsibilities and their families must be supported while training is in progress. The greater potential return from training younger men may, however, be illusory, since such evidence as there is suggests that young men are likely to give shorter service than older men (11).

Failure to retrain our older men may, in the short run, be to the interest of private industry; but it will be against the interest of the nation as a whole, and in the long run, of private industry itself. It may well be that men should be given training in government centers on grounds of their age alone, in the same way as training is given to those who suffer from severe physical disabilities.

All this presupposes that it is possible to retrain older workers, and here we are on very shaky ground indeed. Very little is known of the extent to which retraining can be carried out or of the kind of skills in which retraining is possible.

RE-EMPLOYMENT PROSPECTS

The difficulty of older men in obtaining reemployment is one of the few problems in industrial gerontology which has thus far received attention. The Watkinson Committee (13), for instance, pointed out that Labour Exchanges found older men more difficult to place; that many jobs were controlled by arbitrary age limits; that some pension schemes discriminate against older entrants and in some instances almost prevent their employment; that in the event of a general trade recession or local redundancy in individual firms or industry older men are usually the first to lose their jobs. These, however, are largely administrative problems, in which decisions are made on the basis of custom; they are really effects rather than causes, and while discussion may be valuable, these problems are not likely to be solved until some of their causes have been overcome.

It seems fairly evident that if a man has left his employment voluntarily because he has found the work too difficult or the pace too fast, he will not want to seek another post with similar difficulty. Yet this is usually the only possibility open to him, since it is the only job he knows. Alternatively, if a man has been discharged from a job because he can no longer give the service expected, the same reason will make it unlikely that other employers will take him on. He will be faced with the same alternatives as the man who left voluntarily.

In theory, when skilled labor is scarce, most employers will engage any man who can do the task required of him irrespective of his age. This brings us back again, however, to the problem of the design of the work and to its pace. Again it seems quite probable that good work design, since it should increase the employability of the older man, will help solve some of the problems of re-employment.

If, during a period of full employment, older men find it difficult to get jobs, it is even worse for them when there is some measure of unemployment. Murrell, Griew, and Tucker (11) have shown that men aged 57 to 64 are 65 per cent more likely to lose their jobs during a redundancy than are men under 50; and there is reason to suppose that they would be the first to go should there be a recession. One thing seems clear: that a man thrown out of work at 55 for, say, three years will find it much more difficult to get back into employment than would a man of 25. A similar situation may well arise when automation is introduced, or when a merger takes place (15).

Employers can hardly be blamed for thinking that younger men are likely to be more worth retaining than older men, since through experience or custom this view has become commonly accepted. Unfortunately, there is very little real evidence on the relative merits of older and younger men. There is some evidence that older men will give one-third longer service than younger men before leaving voluntarily (11) and that they are not adversely affected by the heaviness of a job (1), but data on accidents (4, 6, 7), absence, time keeping, quality of work or productivity are either conflicting or scanty. Nor is sufficient yet known of the ability of older men to learn new skills.

CONCLUSION

From middle age onward many men find their work becoming progressively more difficult. It should be the object of industrial gerontology to search for the causes of difficulty and where possible to recommend remedies. From

what has been said it will have been realized that a major cause of difficulty for older workers is the nature or organization of the work. Clearly, jobs planned so that men can continue without strain until final retirement will eliminate problems of re-employment and retraining and, possibly also, of ill health. This, however, cannot be immediately or completely realized. The present need is for research on the various topics discussed above. The most important of these would seem to be:

1. What are the factors in the work situation which cause difficulties to older men? How can they be remedied?
2. What avoidable long term health hazards (other than toxic hazards) are present in a work situation?
3. What is the effect of bonus schemes on older men?
4. What are the determining factors in promotion and how do they discriminate against the older man? What is the role of "status" in job satisfaction?
5. To what extent can older men be retrained? What age group is, economically, most worth training?
6. What is the basis of discrimination against older workers in employment policy? What are the attributes of older men which make them worth employing?
7. What is happening to men who give up their accustomed jobs because they can no longer cope with them? What can be done to help men over their first and subsequent retirements? What is the extent of the skill lost to the community due to these retirements? What are the economic consequences?
8. What are the bases of the present attitudes of industry toward the older worker? What is needed to alter these attitudes and to produce personnel policies more sympathetic to older workers?

These questions, by no means an exhaustive list, imply an enormous program of research. Yet, if interest in industrial gerontology develops at a rate comparable with that already existing in other gerontological fields, there is no reason why substantial advances should not be made in the foreseeable future.

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A NOTE ON LEVEL-OF-ASPIRATION BEHAVIOR AND AGING

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Techniques for studying levels of aspiration have been used in a variety of ways for a variety of purposes. Studies relating aspirational levels to social class (5), to cultural comparisons (8), to adjustment (2), to physical status (9), and to personality variables (3, 10) are noted in the literature.

The present study explores the relation between aging and goal-setting, or level-of-aspiration, behavior. It was felt that an investigation in a specific psychological area could shed some light on a function which may be related directly to the aging process.

METHOD

The technique described by Rotter (6) was used in this study without modification. The apparatus consisted of a board with a grooved center, on either side of which were visibly marked numbers representing scores; a one-inch steel ball; and a miniature cue. Scores range in ascending and descending order from a mid-point of 10 to an end point of 0. The subject is asked to hit the ball with the cue and to try for as high a score as possible.

After a series of practice trials (a "trial" is the total score for five hits), the subject is told that, before each trial begins, he is to estimate the score he expects to get. He is told further that he will be credited for this score if he reaches or exceeds his estimate. If he falls below his estimate, he is penalized two points for each point he falls below. Each subject is required to complete a series of 20 trials.

From among the residents of a Veterans Administration Domiciliary, 39 white males, ranging in age from 70 to 86, were selected on the basis of two criteria: 1) absence of psychiatric disorder, 2) physical disability not disabling enough to prevent participation in the task. Each of these veterans, although physically disabled to some extent, was fully ambulant and capable of self-care. The group had an average of approximately eighth-grade education, ranging from no formal schooling to medical school graduation. Five college graduates were included in the group. Although the occupational achievements of the majority were along semiskilled lines, the group included two retired physicians, a lawyer, a detective, an engineer, a draftsman, and a chemist.

A group of 36 white, male, nursing assistants, who ranged in age from 22 to 36 and who had an average of approximately ninth-grade education (ranging from fifth grade to first-year college), was utilized for comparative purposes.

Comparisons between the groups were made on the following measures:

1. *Discrepancy (D) score.*—The mean of the difference between each trial performance and subsequent estimate in the series of twenty trials.

2. *Shifts.*—The total number of changes in estimate made during the series.

3. *Repression (R)*—The number of times during a series in which a subject forgot to estimate his score.

4. *Pattern analysis.*—Analysis of total response of individual performances. Included in the analyses are levels of estimation and performance; the frequency, direction, and nature of shifts in relation to successful and unsuccessful performance; and test behavior.

We followed Rotter's schematic presentation (6), in which patterns of response are described briefly as follows:

1. *Low positive D-score pattern.*—Subject estimates somewhat higher than past performance, adjusts to success or failure.

2. *Low negative or very slightly positive D-score pattern.*—Estimate is slightly lower than in the first pattern, with subject displaying more cautiousness in approach.

3. *Medium high D-score pattern.*—Higher estimates, but not out of keeping with reality.

4. *Achievement-following pattern.*—Each estimate close to, or equaling, previous performance.

5. *Step pattern.*—Persistent attachment to original estimate. With an estimate once made, the subject does not lower it and does not adjust to repeated failures except by verbal rationalization.

6. *Very high positive D-score pattern.*—Unrealistically high estimates in terms of past performance, with frequent occurrences of unusual shifts and forgetting to estimate.

7. *High negative D-score pattern.*—Frequent downward shifts after success to avoid possibilities of failure.

8. *Rigid pattern.*—No shifts despite success or failure; non-involvement pattern.

9. *Confused or breakdown pattern.*—Unpredictable performance; no consistency in actions.

The nine patterns range in order from socially acceptable to socially unacceptable modes of response to problem situations. The first three patterns appears to represent adequate and acceptable efforts toward self-evaluation of ability in problem-solving. The remaining patterns are reflective of unreal solutions, such as escape from reality, avoidance, severe constriction, limited achievement level.

RESULTS

Table 1 indicates that, despite the considerable difference in age between our young and old groups, performance in many of the measured areas was fairly close. Ability to perform the task, as measured by performance scores, was essentially similar. Quantitative aspiration levels, as measured by discrepancy-scores, were practically equal for both groups. However, a trend toward fewer shifts in estimate by the older group was apparent.

TABLE 1. COMPARISONS BETWEEN 39 OLD AND 36 YOUNG SUBJECTS ON PERFORMANCE AND ASPIRATION MEASURES.

Measure	Old Subjects	Young Subjects
1. Performance score:		
Mean	22.4	22.1
Standard deviation	4.8	3.3
2. Discrepancy score:		
Mean	1.06	.70
Standard deviation	5.17	2.90
3. Shifts:		
Mean number	6.03	7.81
Standard deviation	4.83	4.99
4. Per cent of successful trials	48	52
5. Percent of shifts after:		
Success	16	23*
Failure	15	19
6. Per cent of unusual shifts	6	3*
7. Mean discrepancy score of subjects with more:		
Success than failure (18 old subjects, 19 young subjects)	-3.00	- .55*
Failure than success (21 old subjects, 17 young subjects)	5.49	2.78*
8. Per cent forgetting estimate one or more times:		
Total (191 repressions for old subjects, 36 for young subjects)	90	47*
After success (18 old subjects, 5 young subjects)	51	33
After failure (17 old subjects, 11 young subjects)	49	67
9. Mean discrepancy score of subjects forgetting more:		
After success	-1.24	-3.60
After failure	3.42	2.87

* Indicates a measure for which the difference between old and young groups is significant at the .01 level of confidence or beyond.

Although both groups achieved similar per cents of successful trials (performance reaching or exceeding estimate), the older group did not shift estimates as often after success or failure as did the younger group. Despite this lowered incidence of shifting, the older group exhibited significantly more unusual shifts (shifting estimate upward after failure and/or downward after success) than did the younger group.

The discrepancy scores of 18 older and 19 younger subjects who were more successful than unsuccessful during their performances were significantly lower than the scores of those who achieved more failure than success. However, those of the older group who succeeded apparently did so by underestimating their ability to a larger extent than did the young group. Those of the older group who failed more often than they succeeded overestimated their ability to a far greater extent than did the comparable young group.

Forgetting to estimate occurred one or more times during the performance of 35 per cent of the older subjects. This group accounted for 191 repressions (forgetting to estimate), 94 occurring after failure and 97 after success. These figures differed markedly in the younger group. Only 17 (47 per cent) of the younger subjects failed to remember one or more times, for a total of 36 repressions. Twenty-four repressions occurred after failure and 12 after success. The older group tended to forget to estimate proportionately fewer times after failure, and proportionately more times after success, than did the younger group. Furthermore, as many oldsters forgot to estimate following failure (17) as forgot following success (18), while among the younger group twice as many forgot to estimate following failure as forgot following success.

Although differences between the discrepancy scores of the total groups did not appear, significant discrepancy-score differences were found when the scores of those who forgot more frequently after failure were compared with those who forgot more frequently, or as often, after success. The discrepancy scores were significantly lower for the latter group in both old and young subjects, but the performances of both groups in this area were fairly comparable.

Table 2 reveals the results of the analysis of the total response of individual records. We note that only 26 per cent of the older group (10 subjects) utilized the first three socially

acceptable responses. Thus the majority (74 per cent) utilized maladaptive response patterns. This contrasts significantly with the younger group, 24, or 67 per cent, of whom exhibited adequate problem solving methods.

Among the approaches adopted, the rigid pattern (escape or non-involvement) was manifested by 10 oldsters and only 3 of the younger group. Of the 10 oldsters in this group, 3 combined with their rigid approach a high negative pattern, while 3 others combined a very high positive pattern with the rigid approach.

Six of the older group and none of the younger group used the very high discrepancy-score pattern approach alone, while five of the older and two of the younger subjects used the high negative discrepancy-score pattern alone. It can be seen, then, that the setting of "extreme" goals was a characteristic associated more frequently with our older sample. In addition, the only confused or breakdown pattern noted was located in the older group.

The most frequently noted response pattern of the younger group was the low negative or slightly positive discrepancy-score pattern. Sixteen of the younger sample and only 5 of the older group accounted for this type of performance.

CONCLUSIONS AND DISCUSSION

Those reactions most frequently associated with less stable adaptation were located within the older sample. The pattern analysis disclosed that maladaptive responses were utilized by significantly more of the older than of the younger group. Other authors (3, 4, 7) have suggested that defensive reactions, rather than motivation to achieve, may be involved in "extreme" estimates of goal. The more emotionally secure or self-accepting, the closer to reality would be one's self-appraisal. Insecurity, then, may be an emotional factor which would be more characteristic of our older group, and which would account for the greater variety of maladaptive efforts to maintain balance.

TABLE 2. DISTRIBUTION OF RESPONSE PATTERNS OF 39 OLD AND 36 YOUNG SUBJECTS.

Pattern	Old Subjects		Young Subjects	
	Number	Per Cent	Number	Per Cent
1. Low positive discrepancy score	3	8	1	3
2 Low negative or slightly positive discrepancy score	5	13	16	44*
3. Medium high discrepancy score	2	5	7	19
Subtotal	10	26	24	67*
4. Achievement-following	3	8	3	8
5. Step	4	10	4	11
6. Very high positive discrepancy score	6	15	0	0*
7. High negative discrepancy score	5	13	2	6
8. Rigid	10	25	3	8
9. Confused	1	3	0	0
Total	39	100	36	100

* Indicates a pattern for which the difference between old and young groups is significant at the .01 level of confidence or beyond.

This conclusion was implied by the performance of those subjects who succeeded more often than they failed. Although the discrepancy-scores of both young and old successful groups were significantly lower than the discrepancy scores of the failure groups, the difference was greater in the older group. This finding suggests that the older group expressed greater need for self-protection, and for protection against failure. They were able to resolve the issue by making exceedingly low estimates, which would insure success.

In addition, the discrepancy scores were considerably lower for those subjects of both groups who forgot to estimate more frequently following failure than following success. It is suggested that, for both older and younger subjects, need to avoid failure conflicted strongly with the culturally oriented needs for status (high achievement and high aspiration level) and that this conflict resulted in a painful repressible situation.

Again, as a reflection of greater protective needs and less flexibility, the total older group exhibited tendencies to shift estimates less frequently than the total younger group both after success and after failure. This tendency could reflect, on the older group's part, less involvement with momentary triumphs and defeats. Although motivated to react to success and failure, the responsiveness to these stimuli is more constricted outwardly. Yet the older group produced more unusual shifts than did the younger group, again suggesting far greater instability in overall performances.

SUMMARY

The purpose of this study was to investigate possible relations between advanced age and level-of-aspiration behavior. The protocols of

the Rotter Level of Aspiration test obtained from 39 white male domiciliary members ranging in age from 70 to 86 years were compared with protocols obtained from 36 white, male, nursing assistants whose age range was 22-35 years.

It was found that goal levels were similarly low for both groups, that low flexibility in adjusting to success and failure was more characteristic of the older group, that greater need for self-protection and more vulnerability to stress were manifested by the older group, and that more maladaptive and extreme patterns of response were exhibited by the older population.

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PREPARATION TIME AND CHOICE IN RELATION TO AGE DIFFERENCES IN RESPONSE SPEED

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This study is one of a series intended to discover factors relevant to the slowing of psychomotor processes with age. Previous investigations have been concerned with the relation of age differences in response time to such variables as peripheral conduction velocity (2), motivation (4), and set or readiness (3).

Botwinick, Brinley, and Birren (3) reported that age differences in reaction time were increased at short preparatory intervals when these were varied randomly in a series with longer intervals. It was not clear whether this effect was related more directly to the brevity of the intervals or to inaccurate expectancies about the time of the stimulus occurrence. The main purpose of the present study was to determine whether age differences in response time would increase at short intervals even though experimental conditions facilitated accurate expectancies about the time the stimulus for response would occur. A second purpose of the experiment was to compare the relation between age differences in response speed and interval duration in a simple response situation with the same relation in situations in which the subjects had to choose from alternative responses during the intervals.

METHOD

Thirty men served as the subjects. The 15 older subjects ranged in age from 65 to 81 years, and their median age was 70 years. The ages of the 15 younger men ranged from 19 to 32 years, with a median of 20 years. The older subjects were retired community residents. Eleven of the younger men were college students, and 4 were laboratory technicians. The number of years of schooling ranged from 8 to 16 years in the elderly population, with a median of 14 years. The younger group had gone to school from 12 to 18 years, with a median of 14 years.

The main features of the apparatus were a visual stimulus display and two response levers. The stimulus display consisted of four 7-watt frosted lamps which were arranged to form the corners of a square with 4-inch sides. The display was placed about 20 inches directly in front of the subject, at a height midway between his shoulders and his waist and inclined toward him at an angle of 20 degrees with the horizontal. The lever to be operated with the right hand was placed midway between the two lights on the right-hand side of the display square. It could be moved toward either of these lights. The other lever was similarly placed at the left-hand side of the square.

Seated before the stimulus display, the subject grasped the response levers between the thumb and forefinger of either hand. The experimenter began each trial by setting off a "ready" buzzer, which sounded for 0.5 second. A 2.5-second delay followed the buzzer sound. After the delay, one of the stimulus lights came on. The subject then waited until he heard a 1,000-cycle tone of 85-decibel intensity through earphones before moving the proper lever toward the lighted lamp. The movement of the lever turned off both light and tone. Response times were recorded to the nearest .01 second.

Warning intervals, the intervals between the onset of the light and the tone, differed from conventional preparatory intervals or foreperiods because they were preceded by the delay of 2.5 seconds. Warning intervals were held constant for a series of nine trials in each condition of the experiment in order to facilitate accurate judgment of the length of the intervals. The simple response times of every subject were measured with warning intervals of 0.5, 1.0, and 4.0 seconds.

Response times of each subject were measured also in situations that required a choice of alternative responses during the warning interval. In these choice situations the subject could not anticipate the correct response until the beginning of the warning interval because the light indicating the appropriate response was varied randomly in successive trials. Eight elderly and seven young subjects chose from two alterna-

tives while the remaining seven older and eight younger men chose from four alternatives. The warning intervals in the choice conditions were of the same length as those in the simple response conditions.

The subjects were instructed to respond as quickly as possible and were given several practice trials in a situation requiring a choice in order to familiarize them with the task. The order in which conditions succeeded one another were balanced, with older and younger subjects matched for each order used.

RESULTS

Figure 1 indicates the relation of the mean response times to the duration of the warning interval and to the number of alternatives from which the subjects had to choose during these intervals. Each subject was represented by the median value of the nine measurements in each condition.

Age differences in response time increased significantly at the shorter intervals. Variance analyses revealed that the relation between age and the duration of the warning interval was significant in the simple response situation ($p<.05$), in the choice situations with the data from the two-choice and four-choice groups combined ($p<.01$), and for the combined data of simple and choice situations ($p<.01$). Although Figure 1 seems to show that choice increased the age differences at the 0.5 second interval, this increment was not statistically significant. A variance analysis contrasting simple and choice conditions did not reveal significant interactions between age and choice or among age and choice and warning intervals ($p>.05$).

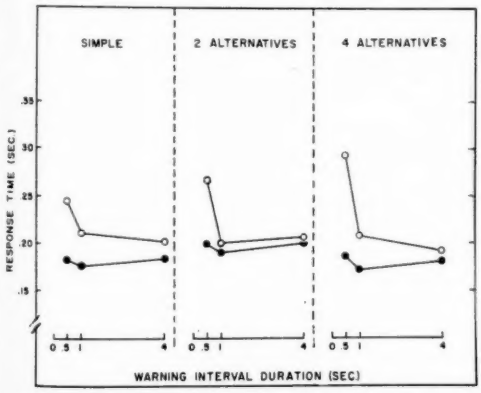

Fig. 1. Mean response times (in seconds) of two age groups in relation to warning interval duration and to number of alternatives in situations requiring choice. Mean response time is based on the median values of individual subjects. The older group (indicated by the lines connecting open dots) was 65-81 years of age; the younger group (indicated by the line connecting solid dots) was 19-32 years.

DISCUSSION

In this study, shortening the warning intervals to 0.5 second resulted in an increase in age differences in response times. The warning intervals were held constant throughout a series of trials, giving the subjects a basis for accurate estimation of the time of stimulus occurrence. The observed increment, therefore, appears to be related directly to the brevity of the interval. The results indicate that older persons needed longer than 0.5 second to get optimally ready to respond.

Since the warning interval was preceded by a 2.5 second delay, it may be argued that in simple response situations the subjects could actually utilize more time than was provided by the warning interval for preparing a response. However, it is not likely that the younger subjects actually needed this time because their response times did not increase at the 0.5 second interval in the choice situations where anticipation was impossible. If older persons, on the other hand, utilized some of the delay period for preparation, this assumption seems to emphasize the point that they needed, or at least used, more time to get optimally set for response.

The interpretation of these results depends upon the extent to which the increased age differences for short intervals could have been eliminated by further practice. Retests of both simple and choice response times with warning intervals of 0.5 seconds were obtained from 9 older and 14 younger subjects. The small amount of practice involved in 9 additional trials lowered mean age differences in response time by .05 second in both the simple and the choice situations. This age difference in practice effect was statistically significant ($p<.05$), and it was greater in magnitude than the original age differences measured at the 1.0 and 4.0 second intervals. Therefore, it was concluded that part of the increase in age differences at the 0.5 second interval reflects a learning difficulty. This experiment does not, of course, indicate whether practice could have completely eliminated the increase in response time at the 0.5-second interval.

Choice was included as a variable in this experiment because discussions of age changes in skills (1, 5, 6) often point to slowness in evaluating a stimulus and in selecting a response as causes of loss of timing ability. If this is true, older persons should have greater difficulty in getting set for a response during a brief warning interval when response preparation involves making a choice than when it does not. Introducing the choice requirement did not, however, increase the age differences in response time by reliable amounts. Failure to obtain an acceptable level of significance for the choice variable may have been due to the small sample. Nevertheless, this experiment suggests that in situations which demand organization of responses within intervals as short as 0.5 second older persons may have difficulty which is not primarily associated with evaluation of the stimulus or with selection of a response.

SUMMARY

Response times of two age groups were measured in conditions which varied the duration of the interval between a warning light and an auditory signal for response. The age groups comprised 15 men aged 65-81 years and 15 men aged 19-32 years. The simple response times were measured for warning intervals of 0.5, 1.0, and 4.0 seconds. In other conditions the subjects were required to choose from either two or four alternative responses during the same warning intervals. Intervals were held constant within a series of trials.

Age differences in response time were increased significantly in both the simple and the choice conditions with 0.5 second intervals. However, responses involving choice did not result in significantly larger age differences than did simple response preparation. Since a small amount of practice reduced the age differences in both simple and choice conditions at the 0.5 second interval, it may be concluded that at least part of the increments for the older persons in the original testing resulted from difficulty in learning to prepare for a response during so brief an interval.

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BOOK REVIEWS

Ageing and Human Skill. By A. T. Welford. London: Oxford University Press, 1958. Pp. vi + 300. $4.00.

Although the author describes this book as a "final report," it differs in many attractive ways from the sort of document that Americans, at least, would expect on the basis of such a description. It is true that the book summarizes the research carried out by some two dozen investigators during the ten-year period from 1946 to 1956 that the Nuffield Unit for Research into Problems of Ageing was a part of the Psychological Laboratory of Cambridge University, but it does a great deal more than that. Welford has included experimental work from this country and elsewhere that is relevant to the work performed at Cambridge; and he has interpreted all the results within the framework of a conceptual model appropriate for the analysis of human skills.

In the first chapter Welford emphasizes the often-neglected fact that performance changes with age are the result of changes in a compensating organism. He conceives the changes as being of essentially two sorts: the deteriorative changes that set in after biological maturity is reached, and which are due to physical and chemical factors, and the usually opposite sorts of changes that result from past experience in dealing with the environment. In other words, skilled performance would be a monotonically increasing function of practice were it not for the deteriorative effects of the biological changes which come with increasing age. The resultant of these two processes is further modified by their interaction with the difficulty level of the task and by certain other parameters such as the relation between the required standard of achievement of the task and the momentary capacity of the performer.

In the second chapter, "On the Nature of Skill," Welford develops the conceptual model of perceptual-motor behavior which serves as the organizing theme for the rest of the book. Between the physical stimulus and the observed response are three quasi-independent processes—*receptor, translation,* and *effector.* Receptor processes include the traditional phenomena of perception and their dependence upon past experience; translation processes provide the transition from input to output and may be regarded as the same sort of processes that others have called decision-making; effector processes are generalized response dispositions rather than specific muscle movements and include such things as rhythms, knacks, and dexterities. These three primary intervening processes are interrelated by feedback mechanisms in such a way that the final output is derived from the concerted action of all. Welford feels that a change in skill can have its locus in any of these processes, and that an important aspect of research in human skills is the attempt to affect these processes differentially.

Although many objections could be raised against this conceptual model as a basis for a theory of perceptual-motor skills, it serves as an excellent descriptive device for organizing the experimental results reported in the remainder of the book. Subsequent chapters deal with the results of investigations on speed and accuracy of movement, pacing, translation tasks, perception, problem solving, learning and memory, and adaptability. Each of these topics is worthy of detailed review, but shortage of space permits only the observation that the research is in general of very high quality, is frequently ingenious, and is reported in a clear and systematic way that makes for quite easy reading.

This book will undoubtedly be of greater interest to the psychologist working on perceptual-motor skills than to the average gerontologist, if only for the reason that few of the research results obtained in the area of human skills so far have clear-cut applications to practical problems of the aged worker. At the same time, the applications which eventually become available will stem from just such basic investigations as these. Furthermore, the descriptive model of behavior developed by Welford will provide those gerontologists who are not specialists in experimental psychology with a conceptual scheme which is nicely balanced between the chaos of unorganized empirical observation and the forbidding mathematics of rigorous hypothetico-deductive theories.

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Organized Religion and the Older Person. Edited by Delton L. Scudder. Gainesville: University of Florida Press, 1958. Pp. 113. $2.50.

This is a report on the Eighth Annual Southern Conference on Gerontology held at the University of Florida in April, 1958. The book contains a Preface, Foreword, eight papers and a Conference Summary. The editor's summary identifies the various threads which run through the papers. These are: 1) Religion defined in terms of its functions; 2) Research reports and the definition of religion in terms of organizational participation; 3) Research reports and minor results; 4) Research difficulties; 5) Earlier preparation for age; and 6) Specific examples of the ministry of organized religion to the aged.

The first two papers, by Hiltner and Barron, indicate the functions organized religion is presumed to perform in the lives of those who have reached later maturity. These are: to help individuals face up to the various losses which have to be met, including loss of life; to help find and maintain a meaningfulness and significance in life; and to help discover and utilize potential values. The next two papers demonstrate some of the ways in which organized religion has served the aged. The first of these, by Entman, relates the philosophy and practice of the Jewish Community; the second, by Poteat, describes the activities of a Protestant (Community) church in Florida which has a large congregation of older persons.

The contributions by Albrecht, Schumacher, and Covalt present the Social, Psychiatric, and Medical aspects of the meaning of religion to older people. The conclusions of each of these papers are essentially the same: although organized religion may have functions to perform for older persons, the primary problem seems to be to get older persons to participate in religious activities. The data presented in these three papers and in Barron's paper indicate that there is no mass flocking of people to churches as they grow older. Women are more active than men in attendance and par-

ticipation in church work; churches are attended more frequently in rural areas than in urban areas; and when one of a church-going couple dies, the remaining spouse frequently participates less than before. The last paper, presented by Blizzard, emphasizes the need of alerting both professional and lay leadership in the churches to the problems of the growing population of older people.

This book clearly demonstrates that most of the research effort reported has been directed toward the general population, and has not been concerned primarily with people in retirement. The little research done specifically for the papers presented here is of a relatively superficial character and adds little to our knowledge about the place of organized religion in the lives of older people. These short-comings are not a reflection on the contributors or on the Conference so much as a demonstration of the lack of professional interest and incentive to carry on research in this area. However, valuable suggestions are made to religious leaders and to scientific investigators concerning church programs and areas of research which could be pursued with profit.

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The Older Worker in Industry. By G. Hamilton Crook and Martin Heinstein. Berkeley: Institute of Industrial Relations, University of California, 1958. Pp. vi + 143. $2.00.

One of the problems which arises to plague an industrial society centers around the entire question of retirement for the society's workers—industrial and otherwise. Provisions of Old Age and Survivors Insurance have at least tended to establish 65 as a compulsory retirement age. Vigorous debate has been carried on as to whether retirement should be compulsory or optional, and if compulsory, at what age it should take place. This debate has taken place in terms of the employer's interests and the interests of society; without much attention being given to the desires of the retiring worker, nor to the possibility that the older worker is being maligned by the proposition that he is no longer valuable to his employer.

The Institute of Industrial Relations at the University of California has been carrying on a long-range study of aging in an industrial society under a grant from the Rockefeller Foundation. Part of that study has consisted of an attempt to determine the attitudes of the workers themselves toward the problems of aging and retirement—an area in which very little work has been done and where very little is known.

This report is based on a survey of 846 industrial workers, skilled, semiskilled, and unskilled, in the San Francisco and Los Angeles areas. A 90-minute interview was held with each worker during which an extensive questionnaire was filled in; company and union records were consulted concerning the employee's work history and productivity; and a supervisor's estimate of each worker was obtained. All available data were analyzed and interpreted to gain information about older workers which might bear upon their optimal utilization in industry. Attention was paid to the worker's attitude toward such things as: jobs and working, age and aging, retirement and the future, and retirement policies. The relation between age and work performance was also considered.

The study does not seem to have produced any startling results, but there are important and interesting indications about the aging process. Surprisingly little evidence was uncovered of a negative attitude on the part of the older worker toward either himself or his job—this in the face of the widely-accepted cliches to the effect that the older worker is slow, accident prone, unproductive, unable to learn, irritable, etc. Of course, the older workers thought of themselves as younger than their chronological age, and did not feel in general that their age handicapped them in the performance of their duties. The study showed that the closer a worker came to retirement age, the less favorably inclined he was towards retirement. Few workers had realistic retirement plans or had made any preparation for retirement. The attitude toward a fixed retirement age, also, tended to become negative with approaching retirement. However, there was a considerable sentiment, even among older groups, towards a fixed retirement age. This sentiment was not explained. Few significant relationships were found between performance measures and aging. There probably are more differences between individuals than between groups, and this highlights the difficulty of making sweeping generalizations concerning aging.

This study, of course, is not definitive, as few studies in such a field can be. It is based on a limited sample and makes no pretense of being other than what it is. Its importance lies in the fact that it attacks a new area in the whole field of aging in an industrial society and lays a firm groundwork on the basis of which much future research can be carried on. A highly desirable result (which may emerge from this line of investigation) would be some kind of an index of aging which could be used to determine the best retirement age for each man, for industry, and for society.

W. P. DILLINGHAM
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The Older Population of the United States. By Henry D. Sheldon. Introduction and summary chapters by Clark Tibbitts. New York: John Wiley and Sons, 1958. Pp. xiii + 223. $6.00.

This is one of the Census Monograph Series, prepared under the auspices of the Social Science Research Council, by the Chief of the Demographic Statistics Branch of the U.S. Bureau of the Census. It uses the 1950 census as a base, and gives many comparisons with demographic data from earlier censuses, with special emphasis on the period since 1900.

There are chapters on age structure, geographic distribution of the older population, employment, occupation, marital status, housing, and income. The study draws upon the major demographic studies of recent years as well as census data for a comprehensive presentation of what is known by demographers concerning older people in the United States. There is recognition that the existing information is inadequate in certain areas, notably those of income and housing arrangements. An interesting section dealing with age distribution in the suburbs shows that the percentage of older people in the suburbs depends upon the age of the suburbs.

The summary chapter by Clark Tibbitts is written more descriptively than the main body of the book and clearly presents the main facts.

This book will serve well as æ convenient single source of demographic data in libraries which want a basic collection of books on gerontology. (Eds.)

Developmental Psychology. By Elizabeth B. Hurlock. 2nd ed. New York: McGraw-Hill Book Co., 1959. Pp. xi + 645. $6.75.

The purpose of this book, to quote from the Preface, is "to give as complete a picture of the developmental changes of the total life span of the normal human being as is possible within the covers of one book." The new edition gives greater attention to the adult portion of the life span than did the original text, which appeared in 1953. After nine chapters devoted to development from conception through late adolescence, there are two chapters each on early adulthood, middle adulthood, and old age.

As indicative of the increased interest of psychologists in the middle and late years, this new edition is a welcome addition to what is as yet a very tiny body of teaching materials available to instructors of undergraduate courses who attempt to deal with post-adolescent development. The book does not, however, present an adequate treatment of adulthood and old age. The two chapters on middle age reflect in part a situation not of the author's making—that there is, in fact, a relative paucity of research findings from which to draw. The author has not, however, sufficiently dealt with the research which does exist, nor does she take a sufficiently tentative approach. These chapters offer many generalizations which, while they may turn out to be correct, are as yet unsupported by research findings. The two chapters on old age suffer from a somewhat different defect, for there is scant justice given to what is now quite a large and respectable research literature on the aged. The approach is given more to value judgments and pessimistic interpretations than to scientific fact.

Perhaps these shortcomings will be outweighed by the fact that as students are stimulated to consider social and psychological development in the adult years, there will appear more research and more textbooks; and that books like this will, in the long run, have a constructive influence on the field of gerontology. (Eds.)

Relationships Within Three-Generation Families. By William M. Smith, Jr., Joseph H. Britton, and Jean O. Britton. (College of Home Economics Research Publication 155.) University Park, Pa.: College of Home Economics, The Pennsylvania State University, April, 1958. Pp. 42.

This is a study of virtually all the three-generation households (97 and 45 respectively) in two Pennsylvania communities; one, an urban community of 10,000 population; the other, a rural village of 2,000. Nearly two-thirds of the households were found to consist of the first generation, their daughter, and her family. In half the cases economic reasons were given as most important in the decision to live together, usually for the benefit of the older generation.

Data were obtained by interviewing a member of each generation within each household on such topics as reasons for living together; financial, physical, and social arrangements; attitudes toward best possible living arrangements for older people; parent-grandparent agreements and disagreements regarding behavior of third-generation members (the majority of whom were teen-agers); factors which children and grandchildren like and dislike about living with parents; and so on. There is also an analysis of the social adjustments of the older persons in relation to several of these factors.

The study is descriptive only (no hypotheses were tested). The data are neither treated with great imaginativeness nor tested for statistical significance. Neither are findings examined in a wider context—for example, it would have been valuable to compare the attitudes of the second- and third-generation groups with those held by persons of similar ages who do not live in three-generation households but for whom similar data are available.

Despite such shortcomings, however, the findings themselves are of considerable interest, given the present dearth of research on three-generation households. To mention only a few such findings, it would appear that attitudes are quite similar in the two communities; that in about half the households, no major problems between the two adult generations are reported; that the youngest generation, while relatively free in expressing disagreements with adults, seem to disagree no more frequently with parents than with grandparents; and that all three generations are quite consistent with regard to the norms governing the behavior of older people. (Eds.)

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Welford, A. T. *Ageing and Human Skill.* London: Oxford University Press, 1958. Pp. vi + 300. $4.00 (reviewed in this issue, page 229).

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Section C

Organization Section
Index to Current Periodical Literature

INDEX TO CURRENT PERIODICAL LITERATURE

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THE SUBJECT categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus, most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given (*B. A.—Biological Abstracts: P. A.—Psychological Abstracts,* and *P. I.—Population Index*). Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the years 1900-1933, 2nd Edition.* For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Branch, Baltimore City Hospitals, Baltimore 24, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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